PREPARED BY PFIZER INC

CDS EFFECTIVE DATE: 19-MAY-2021

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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.

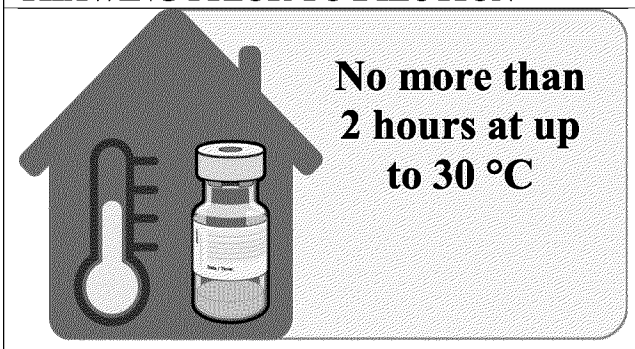
6.5. Nature and contents of container

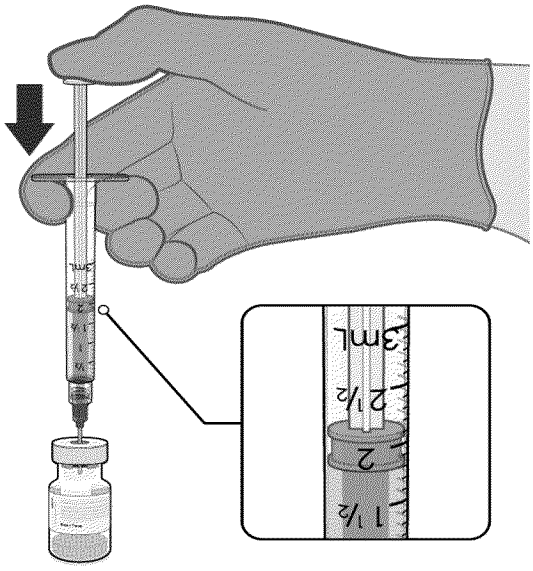
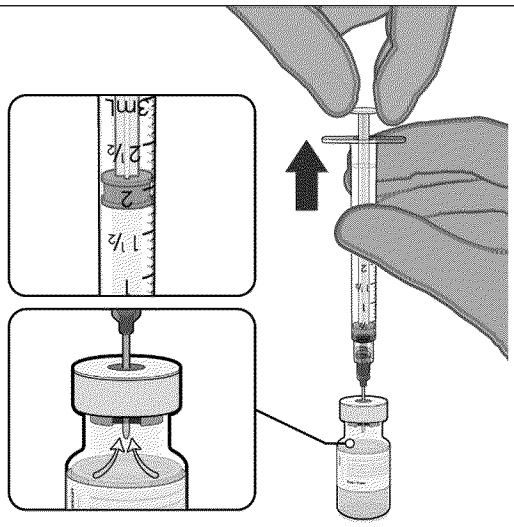
Information to be provided by local subsidiary.

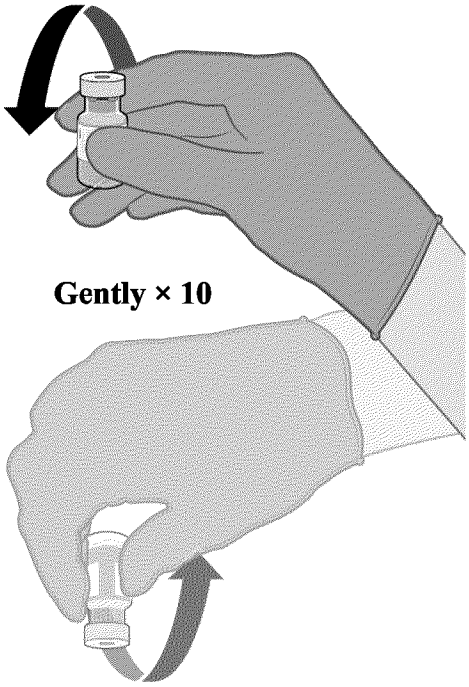
6.6. Special precautions for disposal and other handling[2,3,26,29,30,35,63]

Handling instructions

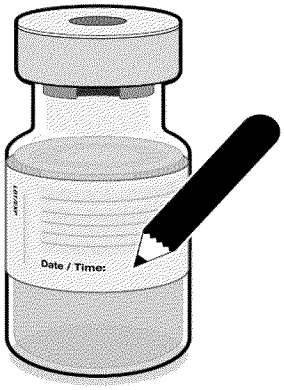
TRADENAME should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

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.

<table>
<tr>
<td> 
</td>
<td>

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.

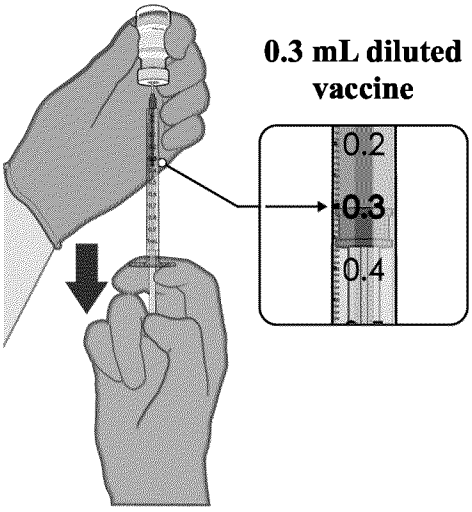
</td>
</tr>
<tr>
<td> 

Record appropriate date and time.
Use within 6 hours after dilution.</td>
<td>

The diluted vials should be marked with the appropriate date and time.
After dilution, store at 2 °C to 30 °C 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.

</td>
</tr>
</table>

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.

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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
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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
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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
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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.

PRODUCT NAME: COVID-19 mRNA Vaccine

CDS Version History:

CDS version number	Effective date	Sections changed
4	19-May-2021	4.4 Special warnings and precautions for use 4.8 Undesirable effects Appendix A Appendix B Appendix C
3	20-Apr-2021	4.8 Undesirable effects
2	02-Mar-2021	4.8 Undesirable effects

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

No safety changes during the reporting period.

4.1 Therapeutic indications

No safety changes during the reporting period.

4.2 Posology and method of administration

No safety changes during the reporting period.

4.3 Contraindications

No safety changes during the reporting period.

4.4 Special warnings and precautions for use

Version 4	Effective Date: 19-May-2021	PfLEET: 2021-0069122 2021-0069099 2021-0069406

Safety/Non-safety: Safety

Content change:

[…]

General recommendations

[…]

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]

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 4	Effective Date: 19-May-2021	PfLEET: 2021-0069122 2021-0069099 2021-0069406

Safety/Non-safety: Safety

Content change:

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 ~~21,720~~22,026 participants 16 years of age or older received at least 1 dose of TRADENAME and a total of ~~21,728~~22,021 participants 16 years of age or older received placebo.[~~13~~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%),[14] fatigue (>60%),[13] headache (>50%),[13] myalgia (>40%), ~~and~~ chills (>30%),[13] arthralgia (>20%),[13] pyrexia[13] and injection site swelling[14] (>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]

[…]

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, ~~based on data up to the cutoff date of 13 March 2021,~~ 2260 adolescents (1131 TRADENAME; 1129 placebo) were 12 ~~to~~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~~fever~~ (>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
~~Immune system disorders~~	~~Anaphylaxis~~ ~~Hypersensitivity reactions (e.g., rash, pruritus, urticaria, angioedema)~~
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

[…]

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)

PRODUCT NAME: COVID-19 mRNA Vaccine

Version 3	Effective Date: 20-Apr-2021	PfLEET: 2021-0068016 2021-0068996

Safety/Non-safety: Safety

Content change:

Summary of safety profile

The safety of TRADENAME was evaluated in participants ~~16~~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. Study C4591001 (Study 2) enrolled approximately ~~44,000~~46,000 participants,[41] 12 years of age or older.[12]

Participants 16 years of age and older
In Study 2, a total of 21,720 participants 16 years of age or older received at least 1 dose of TRADENAME and a total of 21,728 participants 16 years of age or older received placebo.[13]

The most frequent adverse reactions in participants 16 years of age and older (in order from highest to lowest frequencies) were injection site pain ~~at the injection site~~ (>80%),[14] fatigue (>60%),[13] headache (>50%),[13] myalgia and chills (>30%),[13] arthralgia (>20%),[13] pyrexia[13] and injection site swelling[14] (>10%) and were usually mild or moderate in intensity and resolved within a few days after vaccination. 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]

Adolescents 12 through 15 years of age
In an analysis of Study 2, based on data up to the cutoff date of 13 March 2021, 2260 adolescents (1131 TRADENAME; 1129 placebo) were 12 to 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 fever (>20%).[43,44,45]

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

[…]	[…]

~~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]~~

Adverse reactions from TRADENAME post-authorization experience
[…]

Version 2	Effective Date: 02-Mar-2021	PfLEET: 2021-0067666 2021-0067667

Safety/Non-safety: Safety

Content change:
[…]
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
Gastrointestinal disorders	Diarrhea Vomiting
Musculoskeletal and connective tissue disorders	Pain in extremity (arm)

4.9 Overdose
No safety changes during the reporting period.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
No safety changes during the reporting period.

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.

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

Version 4	Effective Date: 19-May-2021	PfLEET: 2021-0069122 2021-0069099 2021-0069406

Safety/Non-safety: Safety

Content change:

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) 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 4	Effective Date: 19-May-2021	PfLEET: 2021-0069122 2021-0069099 2021-0069406

Safety/Non-safety: Safety

Content change:

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

Version 4	Effective Date: 19-May-2021	PfLEET: 2021-0069122 2021-0069099 2021-0069406

Safety/Non-safety: Safety

Content change:

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)
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: 12-FEB-2021

Date of Superseded CDS: NA

COVID-19 mRNA Vaccine

CORE DATA SHEET

VERSION 1

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) disease caused by SARS-CoV-2 virus, in individuals 16 years of age and older.[4]

4.2. Posology and method of administration

Posology

Individuals 16 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]

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 16 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=20,033), 17.1% (n=3434) were 65 through 74 years of age and 4.3% (n=860) were 75 years of age and older (see Section 5.1).[8]

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.

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 16 years of age and older in 2 clinical studies conducted in the United States, Europe, Turkey, South Africa, and South America.[12]
Study BNT162-01 (Study 1) enrolled 60 participants, 18 through 55 years of age.
Study C4591001 (Study 2) enrolled approximately 44,000 participants, 12 years of age or older.[12]

In Study 2, a total of 21,720 participants 16 years of age or older received at least 1 dose of TRADENAME and a total of 21,728 participants 16 years of age or older received placebo.[13]

The most frequent adverse reactions in participants 16 years of age and older (in order from highest to lowest frequencies) were pain at the injection site (>80%),[14] fatigue (>60%),[13] headache (>50%),[13] myalgia and chills (>30%),[13] arthralgia (>20%),[13] pyrexia[13] and injection site swelling[14] (>10%) and were usually mild or moderate in intensity and resolved within a few days after vaccination. A lower frequency of reactogenicity events was associated with greater age.[15]

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

System Organ Class	Adverse Drug Reactions
Blood and lymphatic system disorders	Lymphadenopathy
Immune system disorders	Anaphylaxis Hypersensitivity reactions (e.g., rash, pruritus, urticaria, angioedema)
Nervous system disorders	Headache
Gastrointestinal disorders	Nausea
Musculoskeletal and connective tissue disorders	Arthralgia Myalgia
General disorders and administration site conditions	Pyrexia Chills Malaise Fatigue Injection site pain Injection site swelling Injection site redness

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]

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 disease.[19,20]

Efficacy in participants 16 years of age and older

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 disease.[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]

In the Phase 2/3 portion approximately 44,000 participants 12 years of age and older were randomized equally and received 2 doses of COVID-19 mRNA Vaccine or placebo separated by 21 days. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. Participants are planned to be followed for up to 24 months, for assessments of safety and efficacy against COVID-19 disease.[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 2 presents the specific demographic characteristics in the studied population.

Table 2. 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 disease.
   - 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)

Efficacy against COVID-19 disease

At the time of the primary efficacy analysis, participants had been followed for symptomatic COVID-19 disease 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 disease including those with 1 or more comorbidities that increase the risk of severe COVID-19 disease [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 3.

Table 3. 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 participants 12 to 15 years of age.
f. Credible interval for 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. 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 important demographic characteristics is presented in Table 4.

Table 4. 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)

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.

The subgroup analyses of vaccine efficacy by risk status in participants is presented in Table 5.

Table 5. 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)
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.

Table 5. 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])

Note: 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.

Efficacy against severe COVID-19

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

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]

**Severe illness from COVID-19 is defined by the study protocol as confirmed COVID-19 and presence of at least 1 of the following:*

- *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.*

Efficacy against severe COVID-19 which is 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]

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.

Once removed from the freezer, the unopened vaccine can be stored for up to 5 days at 2 °C to 8 °C, and up to 2 hours at temperatures up to 30 °C, prior to use.

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

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

Diluted medicinal product

Chemical and physical in-use stability 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.

When you are ready to thaw or use the vaccine

- Open-lid vial trays, or vial trays containing less than 195 vials removed from frozen storage (<-60 °C) may be at room temperature (<25 °C) for up to 3 minutes to remove vials or for transfer between ultra-low-temperature environments.
- Once a vial is removed from the vial tray, it should be thawed for use.
- After vial trays are returned to frozen storage following room temperature exposure, they must remain in frozen storage for at least 2 hours before they can be removed again.

Transportation

If local redistribution of unopened vials is needed, and full trays containing vials cannot be transported at -90 °C to -60 °C, available data support transportation of 1 or more thawed vials at 2 °C to 8 °C for up to 12 hours. Any hours used for transport of unopened vials at 2 °C to 8 °C count against the 120-hour limit for storage at 2 °C to 8 °C.[29]

If local redistribution of diluted medicinal product in vials or syringes is needed, available data support physical and chemical stability during transportation between 2 °C and 30 °C for up to 6 hours. Any hours used for transport of diluted medicinal product in vials or syringes at 2 °C to 30 °C count against the 6-hour limit for storage at 2 °C to 30 °C. Microbiological risks, particularly for prepared dosing syringes, are the responsibility of the preparer during transportation of diluted medicinal product.[30]

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

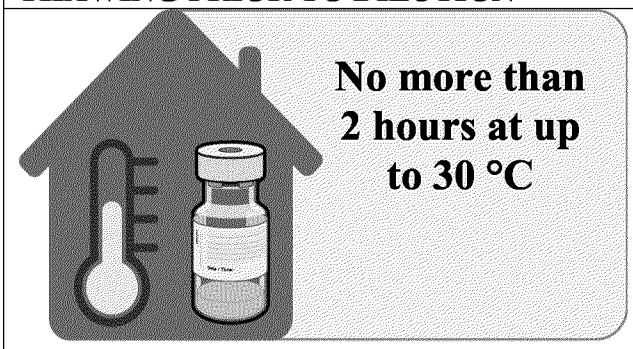
6.5. Nature and contents of container

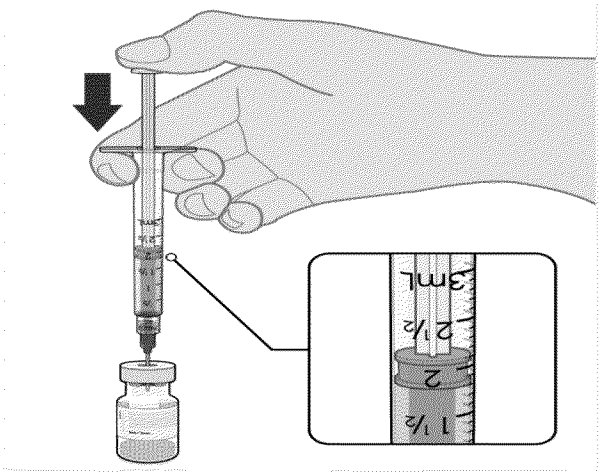
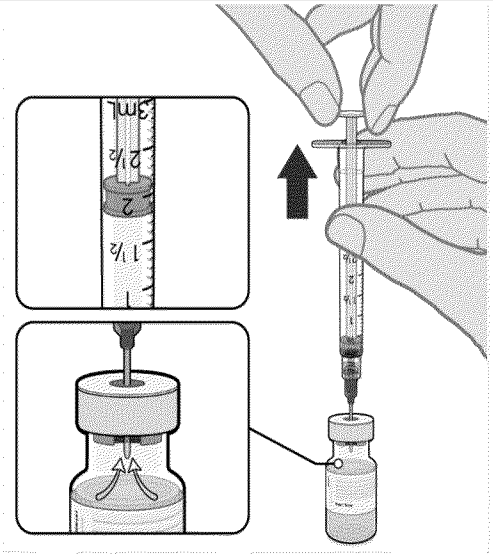
Information to be provided by local subsidiary.

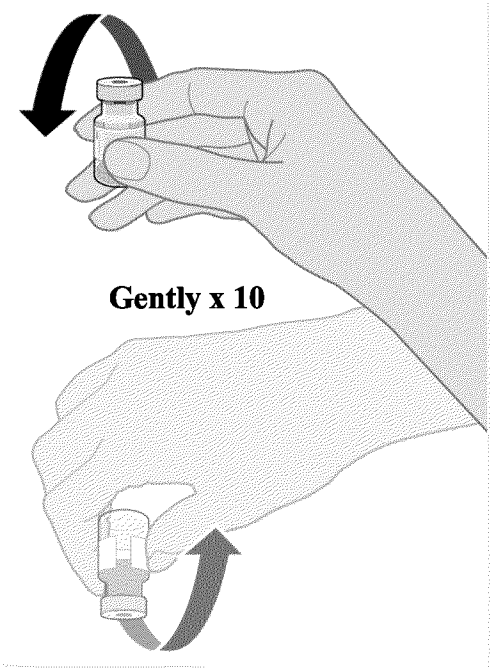
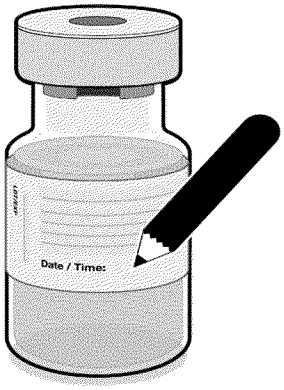
6.6. Special precautions for disposal and other handling[2,3,26,35]

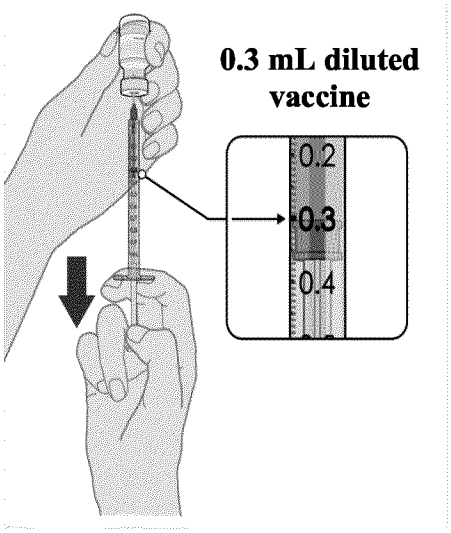
Handling instructions

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. • 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. Discard 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. • 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

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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
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

PREPARED BY PFIZER INC

CDS EFFECTIVE DATE: 02-MAR-2021

Date of Superseded CDS: 12-Feb-2021

COVID-19 mRNA Vaccine

CORE DATA SHEET

VERSION 2

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 16 years of age and older.[4]

4.2. Posology and method of administration

Posology

Individuals 16 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]

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 16 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=20,033), 17.1% (n=3434) were 65 through 74 years of age and 4.3% (n=860) were 75 years of age and older (see Section 5.1).[8]

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.

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 16 years of age and older in 2 clinical studies conducted in the United States, Europe, Turkey, South Africa, and South America.[12]
Study BNT162-01 (Study 1) enrolled 60 participants, 18 through 55 years of age.
Study C4591001 (Study 2) enrolled approximately 44,000 participants, 12 years of age or older.[12]

In Study 2, a total of 21,720 participants 16 years of age or older received at least 1 dose of TRADENAME and a total of 21,728 participants 16 years of age or older received placebo.[13]

The most frequent adverse reactions in participants 16 years of age and older (in order from highest to lowest frequencies) were pain at the injection site (>80%),[14] fatigue (>60%),[13] headache (>50%),[13] myalgia and chills (>30%),[13] arthralgia (>20%),[13] pyrexia[13] and injection site swelling[14] (>10%) and were usually mild or moderate in intensity and resolved within a few days after vaccination. A lower frequency of reactogenicity events was associated with greater age.[15]

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

System Organ Class	Adverse Drug Reactions
Blood and lymphatic system disorders	Lymphadenopathy
Immune system disorders	Anaphylaxis Hypersensitivity reactions (e.g., rash, pruritus, urticaria, angioedema)
Nervous system disorders	Headache
Gastrointestinal disorders	Nausea
Musculoskeletal and connective tissue disorders	Arthralgia Myalgia
General disorders and administration site conditions	Pyrexia Chills Malaise Fatigue Injection site pain Injection site swelling Injection site redness

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]

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
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 in participants 16 years of age and older

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]

In the Phase 2/3 portion approximately 44,000 participants 12 years of age and older were randomized equally and received 2 doses of COVID-19 mRNA Vaccine or placebo separated by 21 days. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. 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)

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

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

Efficacy against COVID-19

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 participants 12 to 15 years of age.
f. Credible interval for 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. 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 important 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)

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.

The subgroup analyses of vaccine efficacy by risk status in participants is presented in Table 6.

Table 6. 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 6. 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.
Note: 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.

Efficacy against severe COVID-19

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

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]

**Severe illness from COVID-19 is defined by the study protocol as confirmed COVID-19 and presence of at least 1 of the following:*

- *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.*

Efficacy against severe COVID-19 which is 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]

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 5 days at 2 °C to 8 °C. Within the 5 days shelf-life at 2 °C to 8 °C, up to 12 hours may be used for transportation.[29] 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.

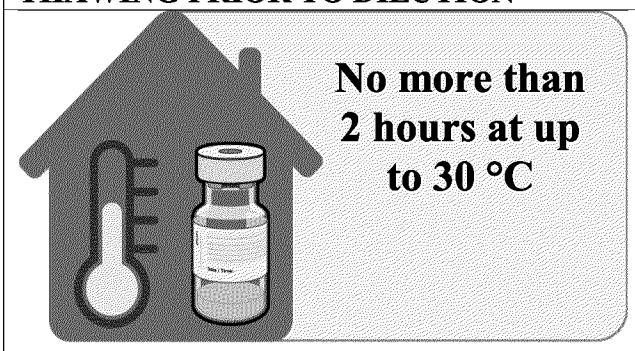
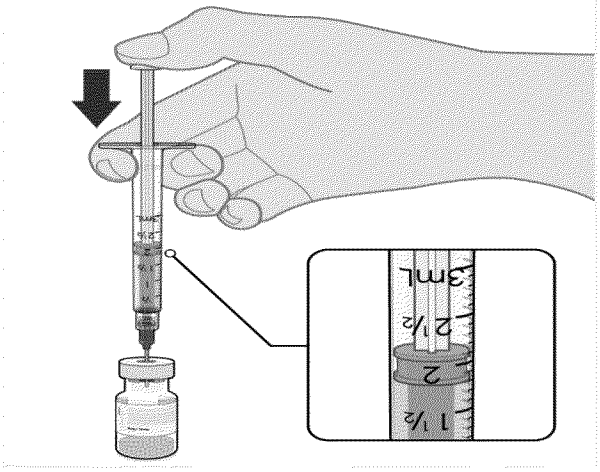
6.5. Nature and contents of container

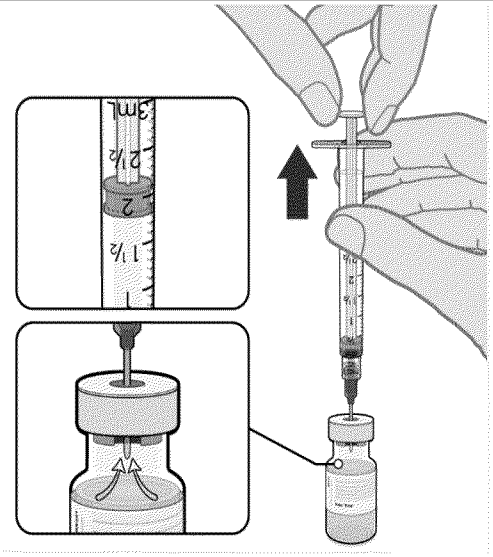
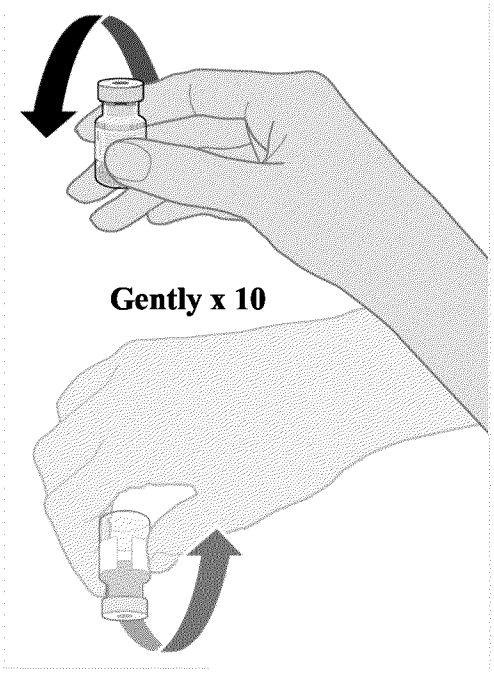
Information to be provided by local subsidiary.

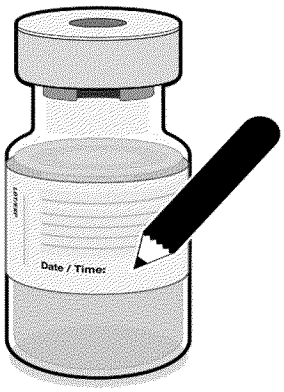
6.6. Special precautions for disposal and other handling[2,3,26,29,30,35]

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 5 days at 2 °C to 8 °C. Within the 5 days 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.

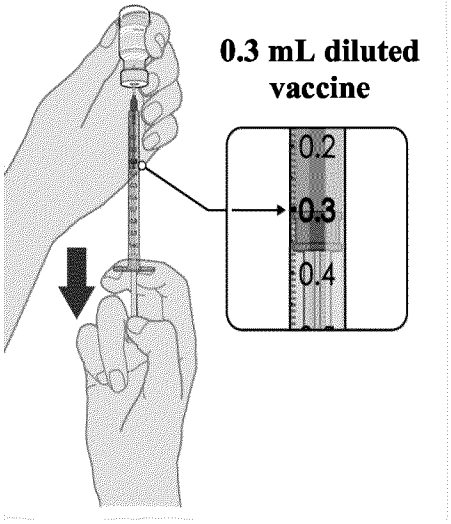
 **Pull back plunger to 1.8 mL to remove air from vial.**	• Equalize vial pressure before removing the needle from the vial stopper by withdrawing 1.8 mL air into the empty diluent syringe.
 **Gently x 10**	• Gently invert the diluted dispersion 10 times. Do not shake. • The diluted vaccine should present 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 °C to 30 °C 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
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

PREPARED BY PFIZER INC

CDS EFFECTIVE DATE: 20-APR-2021

Date of Superseded CDS: 02-Mar-2021

COVID-19 mRNA Vaccine

CORE DATA SHEET

VERSION 3

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=20,033), 17.1% (n=3434) were 65 through 74 years of age and 4.3% (n=860) were 75 years of age and older (see Section 5.1).[8]

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.

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.
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 21,720 participants 16 years of age or older received at least 1 dose of TRADENAME and a total of 21,728 participants 16 years of age or older received placebo.[13]

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%),[14] fatigue (>60%),[13] headache (>50%),[13] myalgia and chills (>30%),[13] arthralgia (>20%),[13] pyrexia[13] and injection site swelling[14] (>10%) and were usually mild or moderate in intensity and resolved within a few days after vaccination. 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]

Adolescents 12 through 15 years of age
In an analysis of Study 2, based on data up to the cutoff date of 13 March 2021, 2260 adolescents (1131 TRADENAME; 1129 placebo) were 12 to 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 fever (>20%).[43,44,45]

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

System Organ Class	Adverse Drug Reactions
Blood and lymphatic system disorders	Lymphadenopathy
Immune system disorders	Anaphylaxis Hypersensitivity reactions (e.g., rash, pruritus, urticaria, angioedema)

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

System Organ Class	Adverse Drug Reactions
Nervous system disorders	Headache
Gastrointestinal disorders	Nausea
Musculoskeletal and connective tissue disorders	Arthralgia Myalgia
General disorders and administration site conditions	Pyrexia Chills 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
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 separated by 21 days. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. 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. Credible interval for 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. 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 important 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)

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.

The subgroup analyses of vaccine efficacy by risk status in participants is presented in Table 6.

Table 6. 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 6. 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.
Note: 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 6. 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.

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

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]

**Severe illness from COVID-19 is defined by the study protocol as confirmed COVID-19 and presence of at least 1 of the following:*

- *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.*

Efficacy against severe COVID-19 which is 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]

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 7.

Table 7. 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 5 days at 2 °C to 8 °C. Within the 5 days shelf-life at 2 °C to 8 °C, up to 12 hours may be used for transportation.[29] 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.

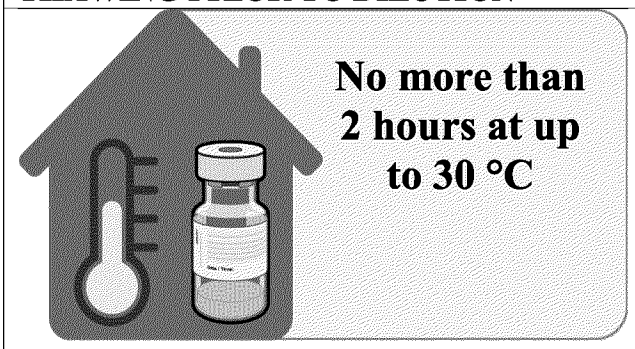
6.5. Nature and contents of container

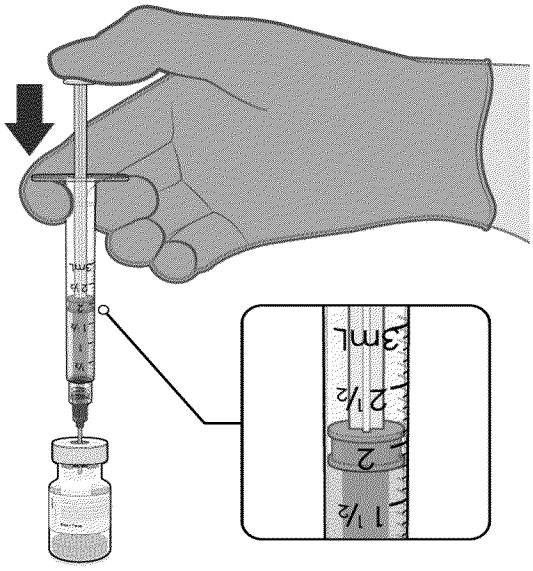
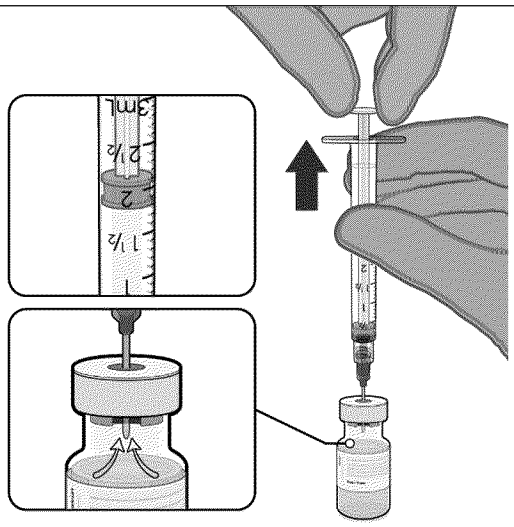
Information to be provided by local subsidiary.

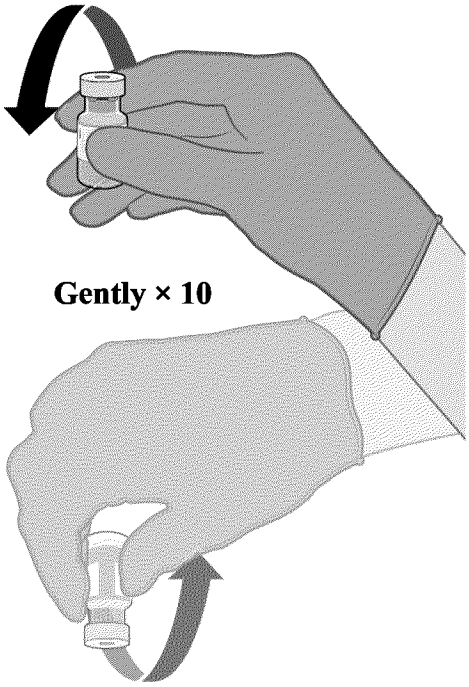
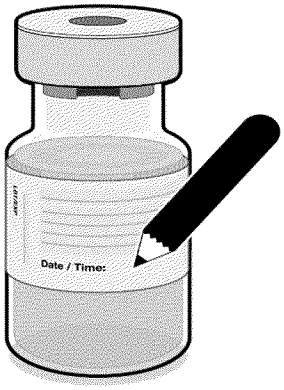
6.6. Special precautions for disposal and other handling[2,3,26,29,30,35]

Handling instructions

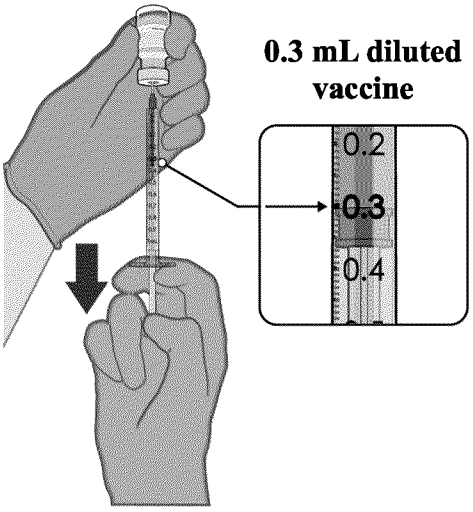
TRADENAME should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

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 5 days at 2 °C to 8 °C. Within the 5 days 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 °C to 30 °C 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

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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
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

FACT SHEET FOR HEALTHCARE PROVIDERS ADMINISTERING VACCINE (VACCINATION PROVIDERS)

EMERGENCY USE AUTHORIZATION (EUA) OF THE PFIZER-BIONTECH COVID-19 VACCINE TO PREVENT CORONAVIRUS DISEASE 2019 (COVID-19)

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product, **Pfizer-BioNTech COVID-19 Vaccine**, for active immunization to prevent COVID-19 in individuals 16 years of age and older.

SUMMARY OF INSTRUCTIONS FOR COVID-19 VACCINATION PROVIDERS

Vaccination providers enrolled in the federal COVID-19 Vaccination Program must report all vaccine administration errors, all serious adverse events, cases of Multisystem Inflammatory Syndrome (MIS) in adults and children, and cases of COVID-19 that result in hospitalization or death following administration of Pfizer-BioNTech COVID-19 Vaccine. See "MANDATORY REQUIREMENTS FOR PFIZER-BIONTECH COVID-19 VACCINE ADMINISTRATION UNDER EMERGENCY USE AUTHORIZATION" for reporting requirements.

The Pfizer-BioNTech COVID-19 Vaccine is a suspension for intramuscular injection administered as a series of two doses (0.3 mL each) 3 weeks apart.

See this Fact Sheet for instructions for preparation and administration. This Fact Sheet may have been updated. For the most recent Fact Sheet, please see www.cvdvaccine.com.

For information on clinical trials that are testing the use of the Pfizer-BioNTech COVID-19 Vaccine for active immunization against COVID-19, please see www.clinicaltrials.gov.

DESCRIPTION OF COVID-19

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the novel coronavirus, SARS-CoV-2, that appeared in late 2019. It is predominantly a respiratory illness that can affect other organs. People with COVID-19 have reported a wide range of symptoms, ranging from mild symptoms to severe illness. Symptoms may appear 2 to 14 days after exposure to the virus. Symptoms may include: fever or chills; cough; shortness of breath; fatigue; muscle or body aches; headache; new loss of taste or smell; sore throat; congestion or runny nose; nausea or vomiting; diarrhea.

DOSAGE AND ADMINISTRATION

Storage and Handling

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

Do not refreeze thawed vials.

Frozen Vials Prior to Use

Cartons of Pfizer-BioNTech COVID-19 Vaccine Multiple Dose Vials arrive in thermal containers with dry ice. Once received, remove the vial cartons immediately from the thermal container and store in an ultra-low temperature freezer between -80ºC to -60ºC (-112ºF to -76ºF). Vials must be kept frozen between -80ºC to -60ºC (-112ºF to -76ºF) and protected from light until ready to use.

If an ultra-low temperature freezer is not available, the thermal container in which the Pfizer-BioNTech COVID-19 Vaccine arrives may be used as temporary storage when consistently re-filled to the top of the container with dry ice. Refer to the re-icing guidelines packed in the original thermal container for instructions regarding the use of the thermal container for temporary storage. The thermal container maintains a temperature range of -90ºC to -60ºC (-130ºF to -76ºF). Storage within this temperature range is not considered an excursion from the recommended storage condition.

Thawed Vials Before Dilution

Thawed Under Refrigeration
Thaw and then store undiluted vials in the refrigerator [2ºC to 8ºC (35ºF to 46ºF)] for up to 5 days (120 hours). A carton of 25 vials or 195 vials may take up to 2 or 3 hours, respectively, to thaw in the refrigerator, whereas a fewer number of vials will thaw in less time.

Thawed at Room Temperature
For immediate use, thaw undiluted vials at room temperature [up to 25ºC (77ºF)] for 30 minutes. Thawed vials can be handled in room light conditions. Vials must reach room temperature before dilution.

Undiluted vials may be stored at room temperature for no more than 2 hours.

Vials After Dilution

- After dilution, store vials between 2°C to 25°C (35°F to 77°F) and use within 6 hours from the time of dilution.
- During storage, minimize exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.
- Any vaccine remaining in vials must be discarded after 6 hours.
- Do not refreeze.

Dosing and Schedule

The Pfizer-BioNTech COVID-19 Vaccine is administered intramuscularly as a series of two doses (0.3 mL each) 3 weeks apart.

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

Dose Preparation

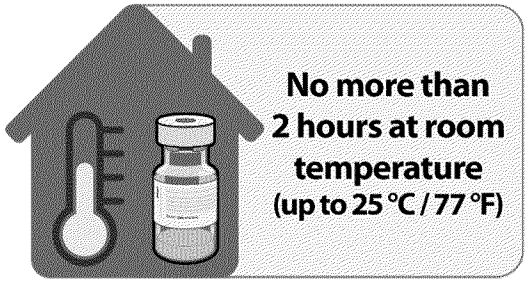
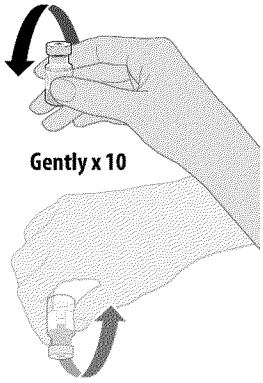
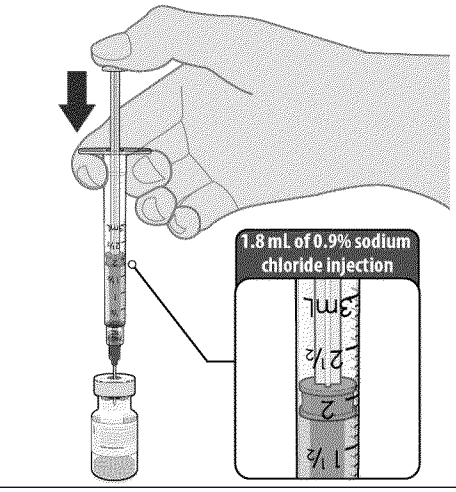
Prior to Dilution

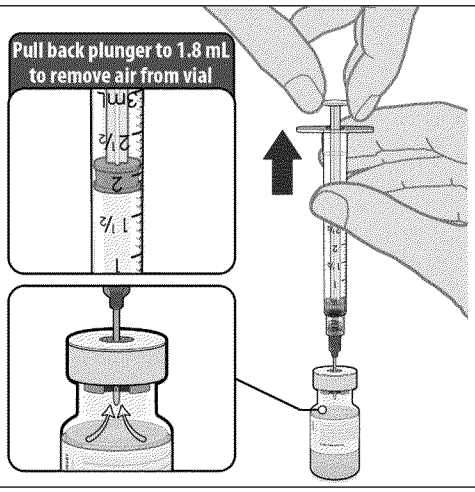
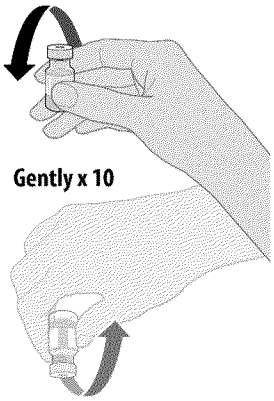
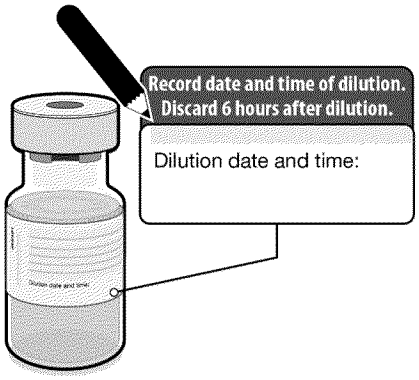
- The Pfizer-BioNTech COVID-19 Vaccine Multiple Dose Vial contains a frozen suspension that does not contain preservative and must be thawed and diluted prior to administration.
- Vials may be thawed in the refrigerator [2ºC to 8ºC (35ºF to 46ºF)] or at room temperature [up to 25ºC (77ºF)] *(see Storage and Handling)*.
- Refer to thawing instructions in the panels below.

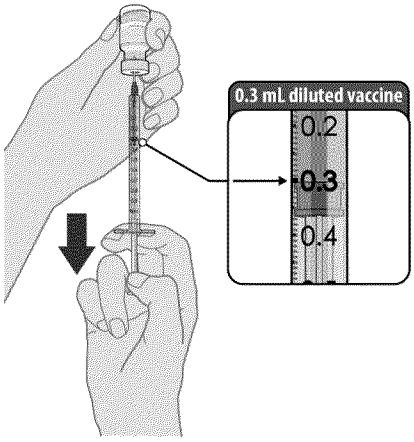
Dilution

Dilute the vial contents using 1.8 mL of 0.9% Sodium Chloride Injection, USP (not provided) to form the Pfizer-BioNTech COVID-19 Vaccine. ONLY use 0.9% Sodium Chloride Injection, USP as the diluent. This diluent is not packaged with the vaccine and must be sourced separately. Do not use bacteriostatic 0.9% Sodium Chloride Injection or any other diluent.

- Refer to dilution and dose preparation instructions in the panels below.

THAWING PRIOR TO DILUTION	
	• Thaw vial(s) of Pfizer-BioNTech COVID-19 Vaccine before use either by: o Allowing vial(s) to thaw in the refrigerator [2ºC to 8ºC (35ºF to 46ºF)]. A carton of vials may take up to 3 hours to thaw, and thawed vials can be stored in the refrigerator for up to five days (120 hours). o Allowing vial(s) to sit at room temperature [up to 25ºC (77ºF)] for 30 minutes. • Using either thawing method, vials must reach room temperature before dilution and must be diluted within 2 hours.
	• Before dilution invert vaccine vial gently 10 times. • Do not shake. • Inspect the liquid in the vial prior to dilution. The liquid is a white to off-white suspension and may contain white to off-white opaque amorphous particles. • Do not use if liquid is discolored or if other particles are observed.
DILUTION	
	• Obtain sterile 0.9% Sodium Chloride Injection, USP. Use only this as the diluent. • Using aseptic technique, withdraw 1.8 mL of diluent into a transfer syringe (21-gauge or narrower needle). • Cleanse the vaccine vial stopper with a single-use antiseptic swab. • Add 1.8 mL of 0.9% Sodium Chloride Injection, USP into the vaccine vial.

	• Equalize vial pressure before removing the needle from the vial by withdrawing 1.8 mL air into the empty diluent syringe.
	• Gently invert the vial containing the Pfizer-BioNTech COVID-19 Vaccine 10 times to mix. • Do not shake. • Inspect the vaccine in the vial. • The vaccine will be an off-white suspension. Do not use if vaccine is discolored or contains particulate matter.
	• Record the date and time of dilution on the Pfizer-BioNTech COVID-19 Vaccine vial label. • Store between 2°C to 25°C (35°F to 77°F). • Discard any unused vaccine 6 hours after dilution.

PREPARATION OF INDIVIDUAL 0.3 mL DOSES OF PFIZER-BIONTECH COVID-19 VACCINE	
	• Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab, and withdraw 0.3 mL of the Pfizer-BioNTech COVID-19 Vaccine. • Administer immediately.

Administration

Visually inspect each dose in the dosing syringe prior to administration. The vaccine will be an off-white suspension. During the visual inspection,

- verify the final dosing volume of 0.3 mL.
- confirm there are no particulates and that no discoloration is observed.
- do not administer if vaccine is discolored or contains particulate matter.

Administer the Pfizer-BioNTech COVID-19 Vaccine intramuscularly.

Contraindications

Do not administer Pfizer-BioNTech COVID-19 Vaccine to individuals with known history of a severe allergic reaction (e.g., anaphylaxis) to any component of the Pfizer-BioNTech COVID-19 Vaccine *(see Full EUA Prescribing Information)*.

Warnings

Appropriate medical treatment used to manage immediate allergic reactions must be immediately available in the event an acute anaphylactic reaction occurs following administration of Pfizer-BioNTech COVID-19 Vaccine.

Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to the Pfizer-BioNTech COVID-19 Vaccine.

Pfizer-BioNTech COVID-19 Vaccine may not protect all vaccine recipients.

Adverse Reactions

Adverse reactions following the Pfizer-BioNTech COVID-19 Vaccine that have been reported in clinical trials include injection site pain, fatigue, headache, muscle pain, chills, joint pain, fever, injection site swelling, injection site redness, nausea, malaise, and lymphadenopathy *(see Full EUA Prescribing Information)*.

Severe allergic reactions have been reported following the Pfizer-BioNTech COVID-19 Vaccine during mass vaccination outside of clinical trials.

Additional adverse reactions, some of which may be serious, may become apparent with more widespread use of the Pfizer-BioNTech COVID-19 Vaccine.

Use with Other Vaccines

There is no information on the co-administration of the Pfizer-BioNTech COVID-19 Vaccine with other vaccines.

INFORMATION TO PROVIDE TO VACCINE RECIPIENTS/CAREGIVERS

As the vaccination provider, you must communicate to the recipient or their caregiver, information consistent with the "Fact Sheet for Recipients and Caregivers" (and provide a copy or direct the individual to the website www.cvdvaccine.com to obtain the Fact Sheet) prior to the individual receiving Pfizer-BioNTech COVID-19 Vaccine, including:

- FDA has authorized the emergency use of the Pfizer-BioNTech COVID-19 Vaccine, which is not an FDA-approved vaccine.
- The recipient or their caregiver has the option to accept or refuse Pfizer-BioNTech COVID-19 Vaccine.
- The significant known and potential risks and benefits of Pfizer-BioNTech COVID-19 Vaccine, and the extent to which such risks and benefits are unknown.
- Information about available alternative vaccines and the risks and benefits of those alternatives.

For information on clinical trials that are testing the use of the Pfizer-BioNTech COVID-19 Vaccine to prevent COVID-19, please see www.clinicaltrials.gov.

Provide a vaccination card to the recipient or their caregiver with the date when the recipient needs to return for the second dose of Pfizer-BioNTech COVID-19 Vaccine.

MANDATORY REQUIREMENTS FOR PFIZER-BIONTECH COVID-19 VACCINE ADMINISTRATION UNDER EMERGENCY USE AUTHORIZATION

In order to mitigate the risks of using this unapproved product under EUA and to optimize the potential benefit of Pfizer-BioNTech COVID-19 Vaccine, the following items are required. Use of unapproved Pfizer-BioNTech COVID-19 Vaccine for active immunization to prevent COVID-19 under this EUA is limited to the following (all requirements **must** be met):

1. Pfizer-BioNTech COVID-19 Vaccine is authorized for use in individuals 16 years of age and older.

2. The vaccination provider must communicate to the individual receiving the Pfizer-BioNTech COVID-19 Vaccine or their caregiver, information consistent with the "Fact Sheet for Recipients and Caregivers" prior to the individual receiving Pfizer-BioNTech COVID-19 Vaccine.

3. The vaccination provider must include vaccination information in the state/local jurisdiction's Immunization Information System (IIS) or other designated system.

4. The vaccination provider is responsible for mandatory reporting of the following to the Vaccine Adverse Event Reporting System (VAERS):
   - vaccine administration errors whether or not associated with an adverse event,
   - serious adverse events* (irrespective of attribution to vaccination),
   - cases of Multisystem Inflammatory Syndrome (MIS) in adults and children, and
   - cases of COVID-19 that result in hospitalization or death.

   Complete and submit reports to VAERS online at https://vaers.hhs.gov/reportevent.html or by calling 1-800-822-7967. The reports should include the words "Pfizer-BioNTech COVID-19 Vaccine EUA" in the description section of the report.

5. The vaccination provider is responsible for responding to FDA requests for information about vaccine administration errors, adverse events, cases of MIS in adults and children, and cases of COVID-19 that result in hospitalization or death following administration of Pfizer-BioNTech COVID-19 Vaccine to recipients.

* Serious adverse events are defined as:
- Death;
- A life-threatening adverse event;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect;

- An important medical event that based on appropriate medical judgement may jeopardize the individual and may require medical or surgical intervention to prevent one of the outcomes listed above.

OTHER ADVERSE EVENT REPORTING TO VAERS AND PFIZER INC.

Vaccination providers may report to VAERS other adverse events that are not required to be reported using the contact information above.

To the extent feasible, report adverse events to Pfizer Inc. using the contact information below or by providing a copy of the VAERS form to Pfizer Inc.

Website	Fax number	Telephone number
www.pfizersafetyreporting.com	1-866-635-8337	1-800-438-1985

ADDITIONAL INFORMATION

For general questions, visit the website or call the telephone number provided below.

To access the most recent Pfizer-BioNTech COVID-19 Vaccine Fact Sheets, please scan the QR code provided below.

Global website	Telephone number
www.cvdvaccine.com	1-877-829-2619 (1-877-VAX-CO19)

AVAILABLE ALTERNATIVES

There is no approved alternative vaccine to prevent COVID-19. There may be clinical trials or availability under EUA of other COVID-19 vaccines.

AUTHORITY FOR ISSUANCE OF THE EUA

The Secretary of Health and Human Services (HHS) has declared a public health emergency that justifies the emergency use of drugs and biological products during the COVID-19 pandemic. In response, FDA has issued an EUA for the unapproved product, Pfizer-BioNTech COVID-19 Vaccine, for active immunization against COVID-19 in individuals 16 years of age and older.

FDA issued this EUA, based on Pfizer-BioNTech's request and submitted data.

Although limited scientific information is available, based on the totality of the scientific evidence available to date, it is reasonable to believe that the Pfizer-BioNTech COVID-19 Vaccine may be effective for the prevention of COVID-19 in individuals as specified in the *Full EUA Prescribing Information*.

This EUA for the Pfizer-BioNTech COVID-19 Vaccine will end when the Secretary of HHS determines that the circumstances justifying the EUA no longer exist or when there is a change in the approval status of the product such that an EUA is no longer needed.

For additional information about Emergency Use Authorization visit FDA at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization.

The Countermeasures Injury Compensation Program

The Countermeasures Injury Compensation Program (CICP) is a federal program that has been created to help pay for related costs of medical care and other specific expenses to compensate people injured after use of certain medical countermeasures. Medical countermeasures are specific vaccines, medications, devices, or other items used to prevent, diagnose, or treat the public during a public health emergency or a security threat. For more information about CICP regarding the Pfizer-BioNTech COVID-19 Vaccine used to prevent COVID-19, visit www.hrsa.gov/cicp, email cicp@hrsa.gov, or call: 1-855-266-2427.

Manufactured by
Pfizer Inc., New York, NY 10017

BIONTECH
Manufactured for
BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

LAB-1450-1.0

Revised: December 2020

END SHORT VERSION FACT SHEET
Long Version (Full EUA Prescribing Information) Begins On Next Page

FULL EMERGENCY USE AUTHORIZATION (EUA) PRESCRIBING INFORMATION

PFIZER-BIONTECH COVID-19 VACCINE

FULL EMERGENCY USE AUTHORIZATION PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full emergency use authorization prescribing information are not listed.

FULL EMERGENCY USE AUTHORIZATION (EUA) PRESCRIBING INFORMATION

1 AUTHORIZED USE

Pfizer-BioNTech COVID-19 Vaccine is authorized for use under an Emergency Use Authorization (EUA) for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older.

2 DOSAGE AND ADMINISTRATION

For intramuscular injection only.

2.1 Preparation for Administration

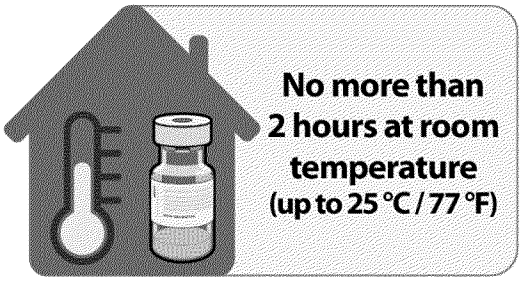
Prior to Dilution

- The Pfizer-BioNTech COVID-19 Vaccine Multiple Dose Vial contains a frozen suspension that does not contain preservative and must be thawed and diluted prior to administration.
- Vials may be thawed in the refrigerator [2°C to 8°C (35°F to 46°F)] or at room temperature [up to 25°C (77°F)] *[see How Supplied/Storage and Handling (19)]*.
- Refer to thawing instructions in the panels below.

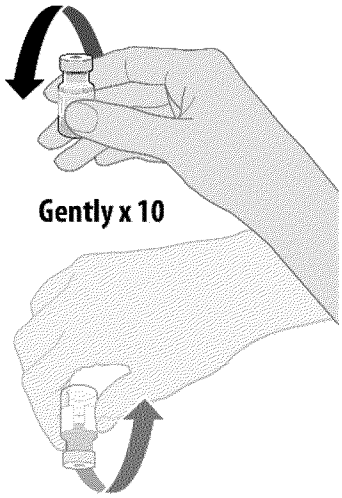
Dilution

- Dilute the vial contents using 1.8 mL of 0.9% Sodium Chloride Injection, USP (not provided) to form the Pfizer-BioNTech COVID-19 Vaccine.
- ONLY use 0.9% Sodium Chloride Injection, USP as the diluent. This diluent is not packaged with the vaccine and must be sourced separately. Do not use bacteriostatic 0.9% Sodium Chloride Injection or any other diluent.
- Refer to dilution and dose preparation instructions in the panels below.

THAWING PRIOR TO DILUTION

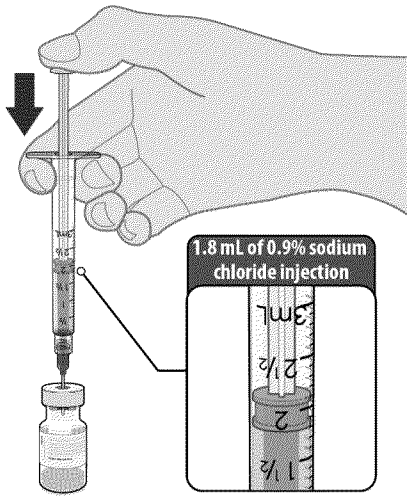


- Thaw vial(s) of Pfizer-BioNTech COVID-19 Vaccine before use either by:
  - Allowing vial(s) to thaw in the refrigerator [2ºC to 8ºC (35ºF to 46ºF)]. A carton of vials may take up to 3 hours to thaw, and thawed vials can be stored in the refrigerator for up to five days (120 hours).
  - Allowing vial(s) to sit at room temperature [up to 25ºC (77ºF)] for 30 minutes.
- Using either thawing method, vials must reach room temperature before dilution and must be diluted within 2 hours.

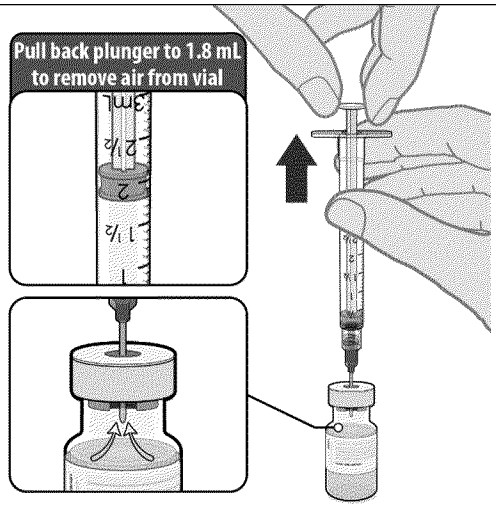
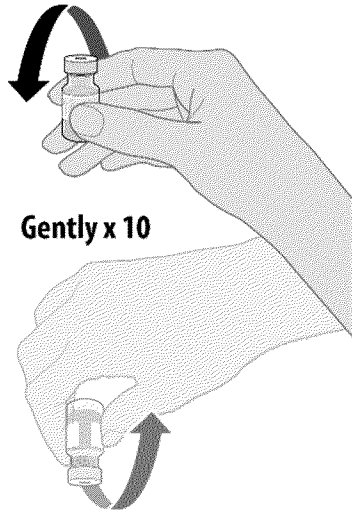
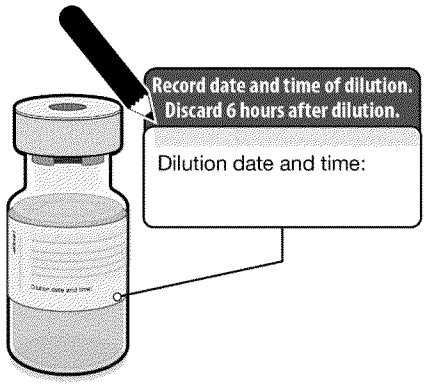


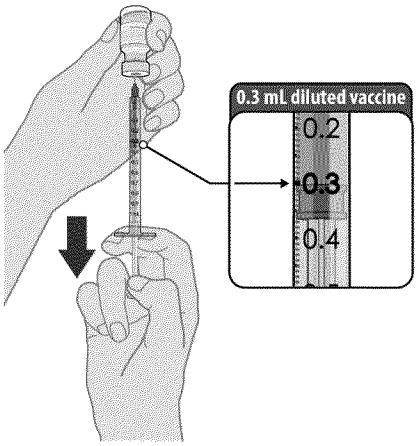
- Before dilution invert vaccine vial gently 10 times.
- Do not shake.
- Inspect the liquid in the vial prior to dilution. The liquid is a white to off-white suspension and may contain white to off-white opaque amorphous particles.
- Do not use if liquid is discolored or if other particles are observed.

DILUTION



- Obtain sterile 0.9% Sodium Chloride Injection, USP. Use only this as the diluent.
- Using aseptic technique, withdraw 1.8 mL of diluent into a transfer syringe (21-gauge or narrower needle).
- Cleanse the vaccine vial stopper with a single-use antiseptic swab.
- Add 1.8 mL of 0.9% Sodium Chloride Injection, USP into the vaccine vial.

	• Equalize vial pressure before removing the needle from the vial by withdrawing 1.8 mL air into the empty diluent syringe.
	• Gently invert the vial containing the Pfizer-BioNTech COVID-19 Vaccine 10 times to mix. • Do not shake. • Inspect the vaccine in the vial. • The vaccine will be an off-white suspension. Do not use if vaccine is discolored or contains particulate matter.
	• Record the date and time of dilution on the Pfizer-BioNTech COVID-19 Vaccine vial label. • Store between 2°C to 25°C (35°F to 77°F). • Discard any unused vaccine 6 hours after dilution.

PREPARATION OF INDIVIDUAL 0.3 mL DOSES OF PFIZER-BIONTECH COVID-19 VACCINE	
	• Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab, and withdraw 0.3 mL of the Pfizer-BioNTech COVID-19 Vaccine. • Administer immediately.

2.2 Administration Information

Visually inspect each dose in the dosing syringe prior to administration. The vaccine will be an off-white suspension. During the visual inspection,

- verify the final dosing volume of 0.3 mL.
- confirm there are no particulates and that no discoloration is observed.
- do not administer if vaccine is discolored or contains particulate matter.

Administer the Pfizer-BioNTech COVID-19 Vaccine intramuscularly.

2.3 Vaccination Schedule for Individuals 16 Years of Age and Older

The Pfizer-BioNTech COVID-19 Vaccine is administered intramuscularly as a series of two doses (0.3 mL each) three weeks apart.

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

3 DOSAGE FORMS AND STRENGTHS

Pfizer-BioNTech COVID-19 Vaccine is a suspension for injection. After preparation, a single dose is 0.3 mL.

4 CONTRAINDICATIONS

Do not administer Pfizer-BioNTech COVID-19 Vaccine to individuals with known history of a severe allergic reaction (e.g., anaphylaxis) to any component of the Pfizer-BioNTech COVID-19 Vaccine *[see Description (13)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Management of Acute Allergic Reactions

Appropriate medical treatment used to manage immediate allergic reactions must be immediately available in the event an acute anaphylactic reaction occurs following administration of Pfizer-BioNTech COVID-19 Vaccine.

5.2 Altered Immunocompetence

Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to the Pfizer-BioNTech COVID-19 Vaccine.

5.3 Limitation of Effectiveness

The Pfizer-BioNTech COVID-19 Vaccine may not protect all vaccine recipients.

6 OVERALL SAFETY SUMMARY

It is MANDATORY for vaccination providers to report to the Vaccine Adverse Event Reporting System (VAERS) all vaccine administration errors, all serious adverse events, cases of Multisystem Inflammatory Syndrome (MIS) in adults and children, and hospitalized or fatal cases of COVID-19 following vaccination with the Pfizer-BioNTech COVID-19 Vaccine. To the extent feasible, provide a copy of the VAERS form to Pfizer Inc. Please see the REQUIREMENTS AND INSTRUCTIONS FOR REPORTING ADVERSE EVENTS AND VACCINE ADMINISTRATION ERRORS section for details on reporting to VAERS and Pfizer Inc.

In clinical studies, adverse reactions in participants 16 years of age and older included pain at the injection site (84.1%), fatigue (62.9%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%), fever (14.2%), injection site swelling (10.5%), injection site redness (9.5%), nausea (1.1%), malaise (0.5%), and lymphadenopathy (0.3%).

Severe allergic reactions have been reported following the Pfizer-BioNTech COVID-19 Vaccine during mass vaccination outside of clinical trials.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of Pfizer-BioNTech COVID-19 Vaccine was evaluated in participants 16 years of age and older in two clinical studies conducted in the United States, Europe, Turkey, South Africa, and South America. Study BNT162-01 (Study 1) was a Phase 1/2, two-part, dose-escalation trial that enrolled 60 participants, 18 through 55 years of age. Study C4591001 (Study 2) is a Phase 1/2/3, multicenter, multinational, randomized, saline placebo-controlled, observer-blind, dose-finding, vaccine candidate-selection (Phase 1) and efficacy (Phase 2/3) study that has enrolled approximately 44,000 participants, 12 years of age or older. Of these, approximately 43,448 participants (21,720 Pfizer-BioNTech COVID-19 Vaccine; 21,728 placebo) in Phase 2/3 are 16 years of age or older (including 138 and 145 adolescents 16 and 17 years of age in the vaccine and placebo groups, respectively).

At the time of the analysis of Study 2 for the EUA, 37,586 (18,801 Pfizer-BioNTech COVID-19 Vaccine and 18,785 placebo) participants 16 years of age or older have been followed for a median of 2 months after the second dose of Pfizer-BioNTech COVID-19 Vaccine.

The safety evaluation in Study 2 is ongoing. The safety population includes participants enrolled by October 9, 2020, and includes safety data accrued through November 14, 2020. Participants 18 years and older in the reactogenicity subset are monitored for solicited local and systemic reactions and use of antipyretic medication after each vaccination in an electronic diary. Participants are being monitored for unsolicited adverse events, including serious adverse events, throughout the study [from Dose 1 through 1 month (all unsolicited adverse events) or 6 months (serious adverse events) after the last vaccination].

Demographic characteristics in Study 2 were generally similar with regard to age, gender, race, and ethnicity among participants who received Pfizer-BioNTech COVID-19 Vaccine and those who received placebo. Overall, among the total participants who received either the Pfizer-BioNTech COVID-19 Vaccine or placebo, 50.6% were male and 49.4% were female, 83.1% were White, 9.1% were Black or African American, 28.0% were Hispanic/Latino, 4.3% were Asian, and 0.5% were American Indian/Alaska Native.

Local and Systemic Adverse Reactions Solicited in the Study 2

Table 1 and Table 2 present the frequency and severity of solicited local and systemic reactions, respectively, within 7 days following each dose of Pfizer-BioNTech COVID-19 Vaccine and placebo in the subset of participants 18 to 55 years of age included in the EUA safety population who were monitored for reactogenicity with an electronic diary.

Table 3 and Table 4 present the frequency and severity of reported solicited local and systemic reactions, respectively, within 7 days of each dose of Pfizer-BioNTech COVID-19 Vaccine and placebo for participants 56 years of age and older.

Across both age groups, the mean duration of pain at the injection site after Dose 2 was 2.5 days (range 1 to 36 days), for redness 2.6 days (range 1 to 34 days), and for swelling 2.3 days (range 1 to 34 days) for participants in the Pfizer-BioNTech COVID-19 Vaccine group.

Solicited reactogenicity data in 16 and 17 year-old participants are limited.

Table 1: Study 2 – Frequency and Percentages of Participants with Solicited Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Participants 18-55 Years of Age‡ – Reactogenicity Subset of the Safety Population*

	Pfizer-BioNTech COVID-19 Vaccine Dose 1 N[a]=2291 n[b] (%)	**Placebo Dose 1 N[a]=2298 n[b] (%)**	**Pfizer-BioNTech COVID-19 Vaccine Dose 2 N[a]=2098 n[b] (%)**	**Placebo Dose 2 N[a]=2103 n[b] (%)**
Redness[c]				
Any (>2 cm)	104 (4.5)	26 (1.1)	123 (5.9)	14 (0.7)
Mild	70 (3.1)	16 (0.7)	73 (3.5)	8 (0.4)
Moderate	28 (1.2)	6 (0.3)	40 (1.9)	6 (0.3)
Severe	6 (0.3)	4 (0.2)	10 (0.5)	0 (0.0)
Swelling[c]				
Any (>2 cm)	132 (5.8)	11 (0.5)	132 (6.3)	5 (0.2)
Mild	88 (3.8)	3 (0.1)	80 (3.8)	3 (0.1)

	Pfizer-BioNTech COVID-19 Vaccine Dose 1 N[a]=2291 n[b] (%)	Placebo Dose 1 N[a]=2298 n[b] (%)	Pfizer-BioNTech COVID-19 Vaccine Dose 2 N[a]=2098 n[b] (%)	Placebo Dose 2 N[a]=2103 n[b] (%)
Moderate	39 (1.7)	5 (0.2)	45 (2.1)	2 (0.1)
Severe	5 (0.2)	3 (0.1)	7 (0.3)	0 (0.0)
Pain at the injection site[d]				
Any	1904 (83.1)	322 (14.0)	1632 (77.8)	245 (11.7)
Mild	1170 (51.1)	308 (13.4)	1039 (49.5)	225 (10.7)
Moderate	710 (31.0)	12 (0.5)	568 (27.1)	20 (1.0)
Severe	24 (1.0)	2 (0.1)	25 (1.2)	0 (0.0)

Note: Reactions were collected in the electronic diary (e-diary) from Day 1 to Day 7 after vaccination.

a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.

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.

‡ Eight participants were between 16 and 17 years of age.

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

Table 2: Study 2 – Frequency and Percentages of Participants with Solicited Systemic Reactions, by Maximum Severity, Within 7 Days After Each Dose – Participants 18-55 Years of Age‡ – Safety Population*

	Pfizer-BioNTech COVID-19 Vaccine Dose 1 N[a]=2291 n[b] (%)	Placebo Dose 1 N[a]=2298 n[b] (%)	Pfizer-BioNTech COVID-19 Vaccine Dose 2 N[a]=2098 n[b] (%)	Placebo Dose 2 N[a]=2103 n[b] (%)
Fever				
≥38.0°C	85 (3.7)	20 (0.9)	331 (15.8)	10 (0.5)
≥38.0°C to 38.4°C	64 (2.8)	10 (0.4)	194 (9.2)	5 (0.2)
>38.4°C to 38.9°C	15 (0.7)	5 (0.2)	110 (5.2)	3 (0.1)
>38.9°C to 40.0°C	6 (0.3)	3 (0.1)	26 (1.2)	2 (0.1)
>40.0°C	0 (0.0)	2 (0.1)	1 (0.0)	0 (0.0)
Fatigue[c]				
Any	1085 (47.4)	767 (33.4)	1247 (59.4)	479 (22.8)
Mild	597 (26.1)	467 (20.3)	442 (21.1)	248 (11.8)
Moderate	455 (19.9)	289 (12.6)	708 (33.7)	217 (10.3)
Severe	33 (1.4)	11 (0.5)	97 (4.6)	14 (0.7)
Headache[c]				
Any	959 (41.9)	775 (33.7)	1085 (51.7)	506 (24.1)
Mild	628 (27.4)	505 (22.0)	538 (25.6)	321 (15.3)
Moderate	308 (13.4)	251 (10.9)	480 (22.9)	170 (8.1)
Severe	23 (1.0)	19 (0.8)	67 (3.2)	15 (0.7)
Chills[c]				
Any	321 (14.0)	146 (6.4)	737 (35.1)	79 (3.8)
Mild	230 (10.0)	111 (4.8)	359 (17.1)	65 (3.1)
Moderate	82 (3.6)	33 (1.4)	333 (15.9)	14 (0.7)
Severe	9 (0.4)	2 (0.1)	45 (2.1)	0 (0.0)

	Pfizer-BioNTech COVID-19 Vaccine Dose 1 N[a]=2291 n[b] (%)	Placebo Dose 1 N[a]=2298 n[b] (%)	Pfizer-BioNTech COVID-19 Vaccine Dose 2 N[a]=2098 n[b] (%)	Placebo Dose 2 N[a]=2103 n[b] (%)
Vomiting[d]				
Any	28 (1.2)	28 (1.2)	40 (1.9)	25 (1.2)
Mild	24 (1.0)	22 (1.0)	28 (1.3)	16 (0.8)
Moderate	4 (0.2)	5 (0.2)	8 (0.4)	9 (0.4)
Severe	0 (0.0)	1 (0.0)	4 (0.2)	0 (0.0)
Diarrhea[e]				
Any	255 (11.1)	270 (11.7)	219 (10.4)	177 (8.4)
Mild	206 (9.0)	217 (9.4)	179 (8.5)	144 (6.8)
Moderate	46 (2.0)	52 (2.3)	36 (1.7)	32 (1.5)
Severe	3 (0.1)	1 (0.0)	4 (0.2)	1 (0.0)
New or worsened muscle pain[c]				
Any	487 (21.3)	249 (10.8)	783 (37.3)	173 (8.2)
Mild	256 (11.2)	175 (7.6)	326 (15.5)	111 (5.3)
Moderate	218 (9.5)	72 (3.1)	410 (19.5)	59 (2.8)
Severe	13 (0.6)	2 (0.1)	47 (2.2)	3 (0.1)
New or worsened joint pain[c]				
Any	251 (11.0)	138 (6.0)	459 (21.9)	109 (5.2)
Mild	147 (6.4)	95 (4.1)	205 (9.8)	54 (2.6)
Moderate	99 (4.3)	43 (1.9)	234 (11.2)	51 (2.4)
Severe	5 (0.2)	0 (0.0)	20 (1.0)	4 (0.2)
Use of antipyretic or pain medication[f]	638 (27.8)	332 (14.4)	945 (45.0)	266 (12.6)

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

a. N = Number of participants reporting at least 1 yes or no response for the specified event after the specified dose.
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.
‡ Eight participants were between 16 and 17 years of age.
* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.

Table 3: Study 2 – Frequency and Percentages of Participants with Solicited Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Participants 56 Years of Age and Older – Safety Population*

	Pfizer-BioNTech COVID-19 Vaccine Dose 1 N[a]=1802 n[b] (%)	Placebo Dose 1 N[a]=1792 n[b] (%)	Pfizer-BioNTech COVID-19 Vaccine Dose 2 N[a]=1660 n[b] (%)	Placebo Dose 2 N[a]=1646 n[b] (%)
Redness[c]				
Any (>2 cm)	85 (4.7)	19 (1.1)	120 (7.2)	12 (0.7)
Mild	55 (3.1)	12 (0.7)	59 (3.6)	8 (0.5)
Moderate	27 (1.5)	5 (0.3)	53 (3.2)	3 (0.2)
Severe	3 (0.2)	2 (0.1)	8 (0.5)	1 (0.1)
Swelling[c]				
Any (>2 cm)	118 (6.5)	21 (1.2)	124 (7.5)	11 (0.7)
Mild	71 (3.9)	10 (0.6)	68 (4.1)	5 (0.3)
Moderate	45 (2.5)	11 (0.6)	53 (3.2)	5 (0.3)
Severe	2 (0.1)	0 (0.0)	3 (0.2)	1 (0.1)
Pain at the injection site[d]				
Any (>2 cm)	1282 (71.1)	166 (9.3)	1098 (66.1)	127 (7.7)
Mild	1008 (55.9)	160 (8.9)	792 (47.7)	125 (7.6)
Moderate	270 (15.0)	6 (0.3)	298 (18.0)	2 (0.1)
Severe	4 (0.2)	0 (0.0)	8 (0.5)	0 (0.0)

Note: Reactions were collected in the electronic diary (e-diary) from Day 1 to Day 7 after vaccination.
a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.
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.
* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.

Table 4: Study 2 – Frequency and Percentages of Participants with Solicited Systemic Reactions, by Maximum Severity, Within 7 Days After Each Dose – Participants 56 Years of Age and Older – Reactogenicity Subset of the Safety Population*

	Pfizer-BioNTech COVID-19 Vaccine Dose 1 N[a]=1802 n[b] (%)	Placebo Dose 1 N[a]=1792 n[b] (%)	Pfizer-BioNTech COVID-19 Vaccine Dose 2 N[a]=1660 n[b] (%)	Placebo Dose 2 N[a]=1646 n[b] (%)
Fever				
≥38.0°C	26 (1.4)	7 (0.4)	181 (10.9)	4 (0.2)
≥38.0°C to 38.4°C	23 (1.3)	2 (0.1)	131 (7.9)	2 (0.1)
>38.4°C to 38.9°C	1 (0.1)	3 (0.2)	45 (2.7)	1 (0.1)
>38.9°C to 40.0°C	1 (0.1)	2 (0.1)	5 (0.3)	1 (0.1)
>40.0°C	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue[c]				
Any	615 (34.1)	405 (22.6)	839 (50.5)	277 (16.8)
Mild	373 (20.7)	252 (14.1)	351 (21.1)	161 (9.8)
Moderate	240 (13.3)	150 (8.4)	442 (26.6)	114 (6.9)
Severe	2 (0.1)	3 (0.2)	46 (2.8)	2 (0.1)

	Pfizer-BioNTech COVID-19 Vaccine Dose 1 N[a]=1802 n[b] (%)	Placebo Dose 1 N[a]=1792 n[b] (%)	Pfizer-BioNTech COVID-19 Vaccine Dose 2 N[a]=1660 n[b] (%)	Placebo Dose 2 N[a]=1646 n[b] (%)
Headache[c]				
Any	454 (25.2)	325 (18.1)	647 (39.0)	229 (13.9)
Mild	348 (19.3)	242 (13.5)	422 (25.4)	165 (10.0)
Moderate	104 (5.8)	80 (4.5)	216 (13.0)	60 (3.6)
Severe	2 (0.1)	3 (0.2)	9 (0.5)	4 (0.2)
Chills[c]				
Any	113 (6.3)	57 (3.2)	377 (22.7)	46 (2.8)
Mild	87 (4.8)	40 (2.2)	199 (12.0)	35 (2.1)
Moderate	26 (1.4)	16 (0.9)	161 (9.7)	11 (0.7)
Severe	0 (0.0)	1 (0.1)	17 (1.0)	0 (0.0)
Vomiting[d]				
Any	9 (0.5)	9 (0.5)	11 (0.7)	5 (0.3)
Mild	8 (0.4)	9 (0.5)	9 (0.5)	5 (0.3)
Moderate	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)
Severe	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Diarrhea[e]				
Any	147 (8.2)	118 (6.6)	137 (8.3)	99 (6.0)
Mild	118 (6.5)	100 (5.6)	114 (6.9)	73 (4.4)
Moderate	26 (1.4)	17 (0.9)	21 (1.3)	22 (1.3)
Severe	3 (0.2)	1 (0.1)	2 (0.1)	4 (0.2)
New or worsened muscle pain[c]				
Any	251 (13.9)	149 (8.3)	477 (28.7)	87 (5.3)
Mild	168 (9.3)	100 (5.6)	202 (12.2)	57 (3.5)
Moderate	82 (4.6)	46 (2.6)	259 (15.6)	29 (1.8)
Severe	1 (0.1)	3 (0.2)	16 (1.0)	1 (0.1)
New or worsened joint pain[c]				
Any	155 (8.6)	109 (6.1)	313 (18.9)	61 (3.7)
Mild	101 (5.6)	68 (3.8)	161 (9.7)	35 (2.1)
Moderate	52 (2.9)	40 (2.2)	145 (8.7)	25 (1.5)
Severe	2 (0.1)	1 (0.1)	7 (0.4)	1 (0.1)
Use of antipyretic or pain medication	358 (19.9)	213 (11.9)	625 (37.7)	161 (9.8)

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

a. N = Number of participants reporting at least 1 yes or no response for the specified event after the specified dose.
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.
* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.

Unsolicited Adverse Events

Serious Adverse Events

In Study 2, among participants 16 to 55 years of age who had received at least 1 dose of vaccine or placebo (Pfizer-BioNTech COVID-19 Vaccine = 10,841; placebo = 10,851), serious adverse events from Dose 1 through up to 30 days after Dose 2 in ongoing follow-up were reported by 0.4% of Pfizer-BioNTech COVID-19 Vaccine recipients and by 0.3% of placebo recipients. In a similar analysis, in participants 56 years of age and older (Pfizer-BioNTech COVID-19 Vaccine = 7960, placebo = 7934), serious adverse events were reported by 0.8% of Pfizer-BioNTech COVID-19 Vaccine recipients and by 0.6% of placebo recipients who received at least 1 dose of Pfizer-BioNTech COVID-19 Vaccine or placebo, respectively. In these analyses, 91.6% of study participants had at least 30 days of follow-up after Dose 2. Appendicitis was reported as a serious adverse event for 12 participants, and numerically higher in the vaccine group, 8 vaccine participants and 4 placebo participants. Currently available information is insufficient to determine a causal relationship with the vaccine. There were no other notable patterns or numerical imbalances between treatment groups for specific categories of serious adverse events (including neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to Pfizer-BioNTech COVID-19 Vaccine.

Non-Serious Adverse Events

Overall in Study 2 in which 10,841 participants 16 to 55 years of age received Pfizer-BioNTech COVID-19 Vaccine and 10,851 participants received placebo, non-serious adverse events from Dose 1 through up to 30 days after Dose 2 in ongoing follow-up were reported in 29.3% of participants who received Pfizer-BioNTech COVID-19 Vaccine and 13.2% of participants in the placebo group, for participants who received at least 1 dose. Overall in a similar analysis in which 7960 participants 56 years of age and older received Pfizer-BioNTech COVID-19 Vaccine, non-serious adverse events within 30 days were reported in 23.8% of participants who received Pfizer-BioNTech COVID-19 Vaccine and 11.7% of participants in the placebo group, for participants who received at least 1 dose. In these analyses, 91.6% of study participants had at least 30 days of follow-up after Dose 2. The higher frequency of reported unsolicited non-serious adverse events among Pfizer BioNTech COVID-19 Vaccine recipients compared to placebo recipients was primarily attributed to local and systemic adverse events reported during the first 7 days following vaccination that are consistent with adverse reactions solicited among participants in the reactogenicity subset and presented in Tables 3 and 4. From Dose 1 through 30 days after Dose 2, reports of lymphadenopathy were imbalanced with notably more cases in the Pfizer-BioNTech COVID-19 Vaccine group (64) vs. the placebo group (6), which is plausibly related to vaccination. Throughout the safety follow-up period to date, Bell's palsy (facial paralysis) was reported by four participants in the Pfizer-BioNTech COVID-19 Vaccine group. Onset of facial paralysis was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of Bell's palsy were reported in the placebo group. Currently available information is insufficient to determine a causal relationship with the vaccine. There were no other notable patterns or numerical imbalances between treatment groups for specific categories of non-serious adverse events (including other neurologic or neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to Pfizer-BioNTech COVID-19 Vaccine.

8 REQUIREMENTS AND INSTRUCTIONS FOR REPORTING ADVERSE EVENTS AND VACCINE ADMINISTRATION ERRORS

See Overall Safety Summary (Section 6) for additional information.

The vaccination provider enrolled in the federal COVID-19 Vaccination Program is responsible for MANDATORY reporting of the listed events following Pfizer-BioNTech COVID-19 Vaccine to the Vaccine Adverse Event Reporting System (VAERS):

- Vaccine administration errors whether or not associated with an adverse event
- Serious adverse events* (irrespective of attribution to vaccination)
- Cases of Multisystem Inflammatory Syndrome (MIS) in children and adults
- Cases of COVID-19 that result in hospitalization or death

*Serious adverse events are defined as:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- An important medical event that based on appropriate medical judgement may jeopardize the individual and may require medical or surgical intervention to prevent one of the outcomes listed above

Instructions for Reporting to VAERS

The vaccination provider enrolled in the federal COVID-19 Vaccination Program should complete and submit a VAERS form to FDA using one of the following methods:

- Complete and submit the report online: https://vaers.hhs.gov/reportevent.html, or
- If you are unable to submit this form electronically, you may fax it to VAERS at 1-877-721-0366. If you need additional help submitting a report you may call the VAERS toll-free information line at 1-800-822-7967 or send an email to info@vaers.org.

IMPORTANT: When reporting adverse events or vaccine administration errors to VAERS, please complete the entire form with detailed information. It is important that the information reported to FDA be as detailed and complete as possible. Information to include:

- Patient demographics (e.g., patient name, date of birth)
- Pertinent medical history
- Pertinent details regarding admission and course of illness
- Concomitant medications
- Timing of adverse event(s) in relationship to administration of the Pfizer-BioNTech COVID-19 Vaccine
- Pertinent laboratory and virology information
- Outcome of the event and any additional follow-up information if it is available at the time of the VAERS report. Subsequent reporting of follow-up information should be completed if additional details become available.

The following steps are highlighted to provide the necessary information for safety tracking:

1. In Box 17, provide information on Pfizer-BioNTech COVID-19 Vaccine and any other vaccines administered on the same day; and in Box 22, provide information on any other vaccines received within one month prior.
2. In Box 18, description of the event:
    a. Write "Pfizer-BioNTech COVID-19 Vaccine EUA" as the first line.
    b. Provide a detailed report of vaccine administration error and/or adverse event. It is important to provide detailed information regarding the patient and adverse event/medication error for ongoing safety evaluation of this unapproved vaccine. Please see information to include listed above.

3. Contact information:
    a. In Box 13, provide the name and contact information of the prescribing healthcare provider or institutional designee who is responsible for the report.
    b. In Box 14, provide the name and contact information of the best doctor/healthcare professional to contact about the adverse event.
    c. In Box 15, provide the address of the facility where vaccine was given (NOT the healthcare provider's office address).

Other Reporting Instructions

Vaccination providers may report to VAERS other adverse events that are not required to be reported using the contact information above.

To the extent feasible, report adverse events to Pfizer Inc. using the contact information below or by providing a copy of the VAERS form to Pfizer Inc.

Website	Fax number	Telephone number
www.pfizersafetyreporting.com	1-866-635-8337	1-800-438-1985

10 DRUG INTERACTIONS

There are no data to assess the concomitant administration of the Pfizer-BioNTech COVID-19 Vaccine with other vaccines.

11 USE IN SPECIFIC POPULATIONS

11.1 Pregnancy

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Available data on Pfizer-BioNTech COVID-19 Vaccine administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

11.2 Lactation

Risk Summary

Data are not available to assess the effects of Pfizer-BioNTech COVID-19 Vaccine on the breastfed infant or on milk production/excretion.

11.3 Pediatric Use

Emergency Use Authorization of Pfizer-BioNTech COVID-19 Vaccine in adolescents 16 and 17 years of age is based on extrapolation of safety and effectiveness from adults 18 years of age and older. Emergency Use Authorization of Pfizer BioNTech COVID-19 Vaccine does not include use in individuals younger than 16 years of age.

11.4 Geriatric Use

Clinical studies of Pfizer-BioNTech COVID-19 Vaccine include participants 65 years of age and older and their data contributes to the overall assessment of safety and efficacy *[see Overall Safety Summary (6.1) and Clinical Trial Results and Supporting Data for EUA (18.1)]*. Of the total number of Pfizer-BioNTech COVID-19 Vaccine recipients in Study 2 (N=20,033), 21.4% (n=4,294) were 65 years of age and older and 4.3% (n=860) were 75 years of age and older.

13 DESCRIPTION

The Pfizer-BioNTech COVID-19 Vaccine is supplied as a frozen suspension in multiple dose vials; each vial must be diluted with 1.8 mL of sterile 0.9% Sodium Chloride Injection, USP prior to use to form the vaccine. Each dose of the Pfizer-BioNTech COVID-19 Vaccine contains 30 mcg of a nucleoside-modified messenger RNA (modRNA) encoding the viral spike (S) glycoprotein of SARS-CoV-2.

Each dose of the Pfizer-BioNTech COVID-19 Vaccine also includes the following ingredients: lipids (0.43 mg (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 0.05 mg 2[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 0.09 mg 1,2-distearoyl-sn-glycero-3-phosphocholine, and 0.2 mg cholesterol), 0.01 mg potassium chloride, 0.01 mg monobasic potassium phosphate, 0.36 mg sodium chloride, 0.07 mg dibasic sodium phosphate dihydrate, and 6 mg sucrose. The diluent (0.9% Sodium Chloride Injection, USP) contributes an additional 2.16 mg sodium chloride per dose.

The Pfizer-BioNTech COVID-19 Vaccine does not contain preservative. The vial stoppers are not made with natural rubber latex.

14 CLINICAL PHARMACOLOGY

14.1 Mechanism of Action

The modRNA in the Pfizer-BioNTech COVID-19 Vaccine is formulated in lipid particles, which enable delivery of the RNA into host cells to allow expression of the SARS-CoV-2 S antigen. The vaccine elicits an immune response to the S antigen, which protects against COVID-19.

18 CLINICAL TRIAL RESULTS AND SUPPORTING DATA FOR EUA

18.1 Efficacy in Participants 16 Years of Age and Older

Study 2 is a multicenter, multinational, Phase 1/2/3, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate–selection, and efficacy study in participants 12 years of age and older. Randomization was stratified by age: 12 through 15 years of age, 16 through 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥56-year stratum. The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19. Participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, were included as were participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV).

In the Phase 2/3 portion approximately 44,000 participants 12 years of age and older were randomized equally and received 2 doses of Pfizer-BioNTech COVID-19 Vaccine or placebo separated by 21 days. Participants are planned to be followed for up to 24 months, for assessments of safety and efficacy against COVID-19.

The population for the analysis of the primary efficacy endpoint included, 36,621 participants 12 years of age and older (18,242 in the Pfizer-BioNTech COVID-19 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. Table 5 presents the specific demographic characteristics in the studied population.

Table 5: Demographics (population for the primary efficacy endpoint)[a]

	Pfizer-BioNTech COVID-19 Vaccine (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 through 15 years	46 (0.3)	42 (0.2)
≥16 through 17 years	66 (0.4)	68 (0.4)
≥16 through 64 years	14,216 (77.9)	14,299 (77.8)
≥65 through 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 disease
- 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)

Efficacy Against COVID-19

The population in the primary efficacy analysis included all participants 12 years of age and older who had been enrolled from July 27, 2020, and followed for the development of COVID-19 through November 14, 2020. Participants 18 to 55 years of age and 56 years of age and older began enrollment from July 27,2020, 16 to 17 years of age began enrollment from September 16, 2020 and 12 to 15 years of age began enrollment from October 15, 2020.

The 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

First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection*			
Subgroup	**Pfizer-BioNTech COVID-19 Vaccine 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 subjects[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 and older	1 0.508 (3848)	19 0.511 (3880)	94.7 (66.7, 99.9)[g]
First COVID-19 occurrence from 7 days after Dose 2 in participants with or without evidence of prior SARS-CoV-2 infection			
Subgroup	**Pfizer-BioNTech COVID-19 Vaccine 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 subjects[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 and older	1 0.530 (4044)	19 0.532 (4067)	94.7 (66.8, 99.9)[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).

* 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 participants 12 to 15 years of age.
f. Credible interval for 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. Confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.

19 HOW SUPPLIED/STORAGE AND HANDLING

Pfizer-BioNTech COVID-19 Vaccine Suspension for Intramuscular Injection, Multiple Dose Vials are supplied in a carton containing 25 multiple dose vials (NDC 59267-1000-3) or 195 multiple dose vials (NDC 59267-1000-2).

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

Do not refreeze thawed vials.

Frozen Vials Prior to Use

Cartons of Pfizer-BioNTech COVID-19 Vaccine Multiple Dose Vials arrive in thermal containers with dry ice. Once received, remove the vial cartons immediately from the thermal container and store in an ultra-low temperature freezer between -80ºC to -60ºC (-112ºF to -76ºF). Vials must be kept frozen between -80ºC to -60ºC (-112ºF to -76ºF) and protected from light, in the original cartons, until ready to use.

If an ultra-low temperature freezer is not available, the thermal container in which the Pfizer-BioNTech COVID-19 Vaccine arrives may be used as temporary storage when consistently re-filled to the top of the container with dry ice. Refer to the re-icing guidelines packed in the original thermal container for instructions regarding the use of the thermal container for temporary storage. The thermal container maintains a temperature range of -90ºC to -60ºC (-130ºF to -76ºF). Storage within this temperature range is not considered an excursion from the recommended storage condition.

Thawed Vials Before Dilution

Thawed Under Refrigeration
Thaw and then store undiluted vials in the refrigerator [2ºC to 8ºC (35ºF to 46ºF)] for up to 5 days (120 hours). A carton of 25 vials or 195 vials may take up to 2 or 3 hours, respectively, to thaw in the refrigerator, whereas a fewer number of vials will thaw in less time.

Thawed at Room Temperature
For immediate use, thaw undiluted vials at room temperature [up to 25ºC (77ºF)] for 30 minutes. Thawed vials can be handled in room light conditions.

Vials must reach room temperature before dilution.

Undiluted vials may be stored at room temperature for no more than 2 hours.

Vials After Dilution

After dilution, store vials between 2°C to 25°C (35°F to 77°F) and use within 6 hours from the time of dilution. During storage, minimize exposure to room light, and avoid exposure to direct sunlight and ultraviolet light. Any vaccine remaining in vials must be discarded after 6 hours. Do not refreeze.

20 PATIENT COUNSELING INFORMATION

Advise the recipient or caregiver to read the Fact Sheet for Recipients and Caregivers.

The vaccination provider must include vaccination information in the state/local jurisdiction's Immunization Information System (IIS) or other designated system. Advise recipient or caregiver that more information about IISs can be found at: https://www.cdc.gov/vaccines/programs/iis/about.html.

21 CONTACT INFORMATION

For general questions, visit the website or call the telephone number provided below.

Website	Telephone number
www.cvdvaccine.com	1-877-829-2619 (1-877-VAX-CO19)

This Full EUA Prescribing Information may have been updated. For the most recent Full EUA Prescribing Information, please see www.cvdvaccine.com.

Manufactured by
Pfizer Inc., New York, NY 10017

Manufactured for
BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

LAB-1457-1.0

Revised: December 2020

FACT SHEET FOR HEALTHCARE PROVIDERS ADMINISTERING VACCINE (VACCINATION PROVIDERS)

EMERGENCY USE AUTHORIZATION (EUA) OF THE PFIZER-BIONTECH COVID-19 VACCINE TO PREVENT CORONAVIRUS DISEASE 2019 (COVID-19)

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product, **Pfizer-BioNTech COVID-19 Vaccine**, for active immunization to prevent COVID-19 in individuals 16 years of age and older.

SUMMARY OF INSTRUCTIONS FOR COVID-19 VACCINATION PROVIDERS

Vaccination providers enrolled in the federal COVID-19 Vaccination Program must report all vaccine administration errors, all serious adverse events, cases of Multisystem Inflammatory Syndrome (MIS) in adults and children, and cases of COVID-19 that result in hospitalization or death following administration of Pfizer-BioNTech COVID-19 Vaccine. See "MANDATORY REQUIREMENTS FOR PFIZER-BIONTECH COVID-19 VACCINE ADMINISTRATION UNDER EMERGENCY USE AUTHORIZATION" for reporting requirements.

The Pfizer-BioNTech COVID-19 Vaccine is a suspension for intramuscular injection administered as a series of two doses (0.3 mL each) 3 weeks apart.

See this Fact Sheet for instructions for preparation and administration. This Fact Sheet may have been updated. For the most recent Fact Sheet, please see www.cvdvaccine.com.

For information on clinical trials that are testing the use of the Pfizer-BioNTech COVID-19 Vaccine for active immunization against COVID-19, please see www.clinicaltrials.gov.

DESCRIPTION OF COVID-19

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the novel coronavirus, SARS-CoV-2, that appeared in late 2019. It is predominantly a respiratory illness that can affect other organs. People with COVID-19 have reported a wide range of symptoms, ranging from mild symptoms to severe illness. Symptoms may appear 2 to 14 days after exposure to the virus. Symptoms may include: fever or chills; cough; shortness of breath; fatigue; muscle or body aches; headache; new loss of taste or smell; sore throat; congestion or runny nose; nausea or vomiting; diarrhea.

DOSAGE AND ADMINISTRATION

Storage and Handling

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

Do not refreeze thawed vials.

Frozen Vials Prior to Use

Cartons of Pfizer-BioNTech COVID-19 Vaccine Multiple Dose Vials arrive in thermal containers with dry ice. Once received, remove the vial cartons immediately from the thermal container and store in an ultra-low temperature freezer between -80°C to -60°C (-112°F to -76°F). Vials must be kept frozen between -80°C to -60°C (-112°F to -76°F) and protected from light until ready to use.

If an ultra-low temperature freezer is not available, the thermal container in which the Pfizer-BioNTech COVID-19 Vaccine arrives may be used as temporary storage when consistently re-filled to the top of the container with dry ice. Refer to the re-icing guidelines packed in the original thermal container for instructions regarding the use of the thermal container for temporary storage. The thermal container maintains a temperature range of -90°C to -60°C (-130°F to -76°F). Storage within this temperature range is not considered an excursion from the recommended storage condition.

Thawed Vials Before Dilution

Thawed Under Refrigeration
Thaw and then store undiluted vials in the refrigerator [2°C to 8°C (35°F to 46°F)] for up to 5 days (120 hours). A carton of 25 vials or 195 vials may take up to 2 or 3 hours, respectively, to thaw in the refrigerator, whereas a fewer number of vials will thaw in less time.

Thawed at Room Temperature
For immediate use, thaw undiluted vials at room temperature [up to 25°C (77°F)] for 30 minutes. Thawed vials can be handled in room light conditions. Vials must reach room temperature before dilution.

Undiluted vials may be stored at room temperature for no more than 2 hours.

Vials After Dilution

- After dilution, store vials between 2°C to 25°C (35°F to 77°F) and use within 6 hours from the time of dilution.
- During storage, minimize exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.
- Any vaccine remaining in vials must be discarded after 6 hours.
- Do not refreeze.

Dosing and Schedule

The Pfizer-BioNTech COVID-19 Vaccine is administered intramuscularly as a series of two doses (0.3 mL each) 3 weeks apart.

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

Dose Preparation

Prior to Dilution

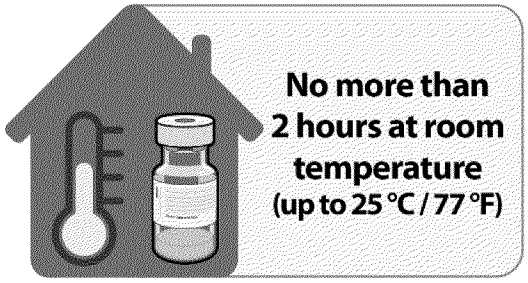
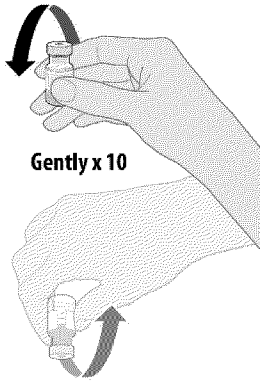
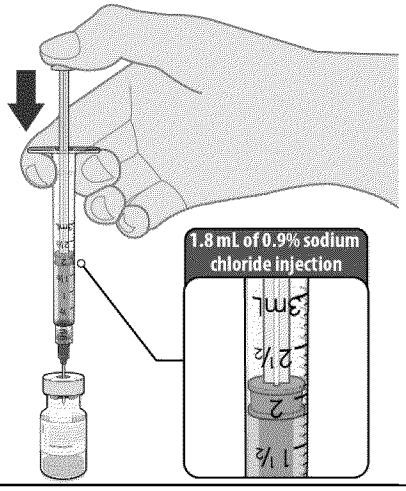
- The Pfizer-BioNTech COVID-19 Vaccine Multiple Dose Vial contains a volume of 0.45 mL, supplied as a frozen suspension that does not contain preservative. Each vial must be thawed and diluted prior to administration.
- Vials may be thawed in the refrigerator [2°C to 8°C (35°F to 46°F)] or at room temperature [up to 25°C (77°F)] *(see Storage and Handling)*.
- Refer to thawing instructions in the panels below.

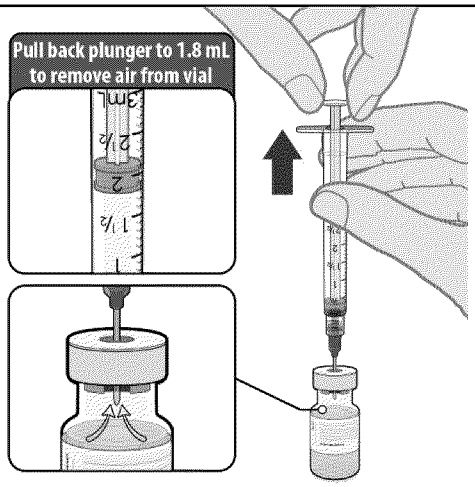
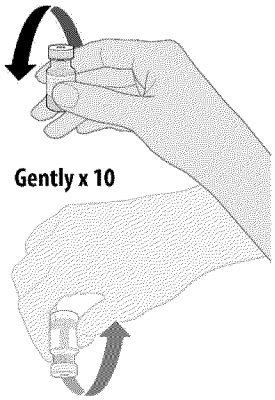
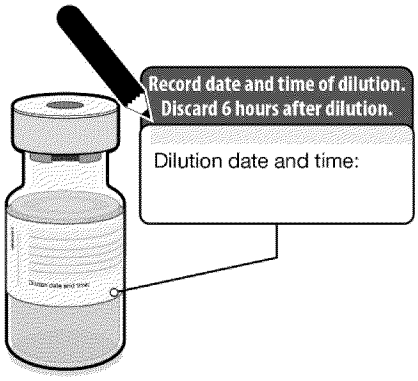
Dilution

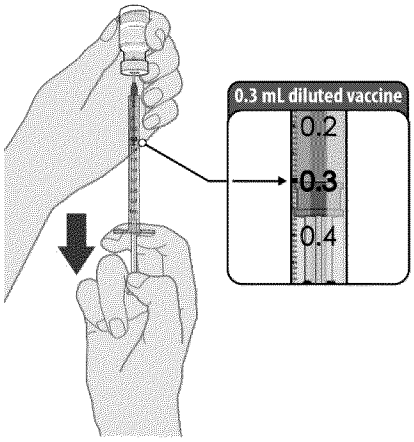
Dilute the vial contents using 1.8 mL of 0.9% Sodium Chloride Injection, USP (not provided) to form the Pfizer-BioNTech COVID-19 Vaccine. ONLY use 0.9% Sodium Chloride Injection, USP as the diluent. This diluent is not packaged with the vaccine and must be sourced separately. Do not use bacteriostatic 0.9% Sodium Chloride Injection or any other diluent. Do not use more than 1.8 mL of diluent.

After dilution, one vial contains up to 6 doses of 0.3 mL. Vial labels and cartons may state that after dilution, a vial contains 5 doses of 0.3 mL. The information on the number of doses per vial after dilution in this Fact Sheet supersedes the number of doses stated on vial labels and cartons.

- Refer to dilution and dose preparation instructions in the panels below.

THAWING PRIOR TO DILUTION	
	• Thaw vial(s) of Pfizer-BioNTech COVID-19 Vaccine before use either by: o Allowing vial(s) to thaw in the refrigerator [2°C to 8°C (35°F to 46°F)]. A carton of vials may take up to 3 hours to thaw, and thawed vials can be stored in the refrigerator for up to five days (120 hours). o Allowing vial(s) to sit at room temperature [up to 25°C (77°F)] for 30 minutes. • Using either thawing method, vials must reach room temperature before dilution and must be diluted within 2 hours.
	• Before dilution invert vaccine vial gently 10 times. • Do not shake. • Inspect the liquid in the vial prior to dilution. The liquid is a white to off-white suspension and may contain white to off-white opaque amorphous particles. • Do not use if liquid is discolored or if other particles are observed.
DILUTION	
	• Obtain sterile 0.9% Sodium Chloride Injection, USP. Use only this as the diluent. • Using aseptic technique, withdraw 1.8 mL of diluent into a transfer syringe (21-gauge or narrower needle). • Cleanse the vaccine vial stopper with a single-use antiseptic swab. • Add 1.8 mL of 0.9% Sodium Chloride Injection, USP into the vaccine vial.

	• Equalize vial pressure before removing the needle from the vial by withdrawing 1.8 mL air into the empty diluent syringe.
	• Gently invert the vial containing the Pfizer-BioNTech COVID-19 Vaccine 10 times to mix. • Do not shake. • Inspect the vaccine in the vial. • The vaccine will be an off-white suspension. Do not use if vaccine is discolored or contains particulate matter.
	• Record the date and time of dilution on the Pfizer-BioNTech COVID-19 Vaccine vial label. • Store between 2°C to 25°C (35°F to 77°F). • Discard any unused vaccine 6 hours after dilution.

PREPARATION OF INDIVIDUAL 0.3 mL DOSES OF PFIZER-BIONTECH COVID-19 VACCINE	
	• Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab, and withdraw 0.3 mL of the Pfizer-BioNTech COVID-19 Vaccine preferentially using a low dead-volume syringe and/or needle. • Administer immediately.

Administration

Visually inspect each dose in the dosing syringe prior to administration. The vaccine will be an off-white suspension. During the visual inspection,

- verify the final dosing volume of 0.3 mL.
- confirm there are no particulates and that no discoloration is observed.
- do not administer if vaccine is discolored or contains particulate matter.

Administer the Pfizer-BioNTech COVID-19 Vaccine intramuscularly.

After preparation, vials of Pfizer-BioNTech COVID-19 Vaccine contain up to six doses of 0.3mL. Low dead-volume syringes and/or needles can be used to extract up to six 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 content.
- Do not pool excess vaccine from multiple vials.

Contraindications

Do not administer Pfizer-BioNTech COVID-19 Vaccine to individuals with known history of a severe allergic reaction (e.g., anaphylaxis) to any component of the Pfizer-BioNTech COVID-19 Vaccine *(see Full EUA Prescribing Information)*.

Warnings

Appropriate medical treatment used to manage immediate allergic reactions must be immediately available in the event an acute anaphylactic reaction occurs following administration of Pfizer-BioNTech COVID-19 Vaccine.

Monitor Pfizer-BioNTech COVID-19 Vaccine recipients for the occurrence of immediate adverse reactions according to the Centers for Disease Control and Prevention guidelines (https://www.cdc.gov/vaccines/covid-19/).

Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to the Pfizer-BioNTech COVID-19 Vaccine.

Pfizer-BioNTech COVID-19 Vaccine may not protect all vaccine recipients.

Adverse Reactions

Adverse reactions following the Pfizer-BioNTech COVID-19 Vaccine that have been reported in clinical trials include injection site pain, fatigue, headache, muscle pain, chills, joint pain, fever, injection site swelling, injection site redness, nausea, malaise, and lymphadenopathy *(see Full EUA Prescribing Information)*.

Severe allergic reactions have been reported following the Pfizer-BioNTech COVID-19 Vaccine during mass vaccination outside of clinical trials.

Additional adverse reactions, some of which may be serious, may become apparent with more widespread use of the Pfizer-BioNTech COVID-19 Vaccine.

Use with Other Vaccines

There is no information on the co-administration of the Pfizer-BioNTech COVID-19 Vaccine with other vaccines.

INFORMATION TO PROVIDE TO VACCINE RECIPIENTS/CAREGIVERS

As the vaccination provider, you must communicate to the recipient or their caregiver, information consistent with the "Fact Sheet for Recipients and Caregivers" (and provide a copy or direct the individual to the website www.cvdvaccine.com to obtain the Fact Sheet) prior to the individual receiving Pfizer-BioNTech COVID-19 Vaccine, including:

- FDA has authorized the emergency use of the Pfizer-BioNTech COVID-19 Vaccine, which is not an FDA-approved vaccine.
- The recipient or their caregiver has the option to accept or refuse Pfizer-BioNTech COVID-19 Vaccine.
- The significant known and potential risks and benefits of Pfizer-BioNTech COVID-19 Vaccine, and the extent to which such risks and benefits are unknown.
- Information about available alternative vaccines and the risks and benefits of those alternatives.

For information on clinical trials that are testing the use of the Pfizer-BioNTech COVID-19 Vaccine to prevent COVID-19, please see www.clinicaltrials.gov.

Provide a vaccination card to the recipient or their caregiver with the date when the recipient needs to return for the second dose of Pfizer-BioNTech COVID-19 Vaccine.

Provide the **v-safe** information sheet to vaccine recipients/caregivers and encourage vaccine recipients to participate in **v-safe**. **V-safe** is a new voluntary smartphone-based tool that uses text messaging and web surveys to check in with people who have been vaccinated to identify potential side effects after COVID-19 vaccination. **V-safe** asks questions that help CDC monitor the safety of COVID-19 vaccines. **V-safe** also provides second-dose reminders if needed and live telephone follow-up by CDC if participants report a significant health impact following COVID-19 vaccination. For more information, visit: www.cdc.gov/vsafe.

MANDATORY REQUIREMENTS FOR PFIZER-BIONTECH COVID-19 VACCINE ADMINISTRATION UNDER EMERGENCY USE AUTHORIZATION

In order to mitigate the risks of using this unapproved product under EUA and to optimize the potential benefit of Pfizer-BioNTech COVID-19 Vaccine, the following items are required. Use of unapproved Pfizer-BioNTech COVID-19 Vaccine for active immunization to prevent COVID-19 under this EUA is limited to the following (all requirements **must** be met):

1. Pfizer-BioNTech COVID-19 Vaccine is authorized for use in individuals 16 years of age and older.

2. The vaccination provider must communicate to the individual receiving the Pfizer-BioNTech COVID-19 Vaccine or their caregiver, information consistent with the "Fact Sheet for Recipients and Caregivers" prior to the individual receiving Pfizer-BioNTech COVID-19 Vaccine.

3. The vaccination provider must include vaccination information in the state/local jurisdiction's Immunization Information System (IIS) or other designated system.

4. The vaccination provider is responsible for mandatory reporting of the following to the Vaccine Adverse Event Reporting System (VAERS):
   - vaccine administration errors whether or not associated with an adverse event,
   - serious adverse events* (irrespective of attribution to vaccination),
   - cases of Multisystem Inflammatory Syndrome (MIS) in adults and children, and
   - cases of COVID-19 that result in hospitalization or death.

   Complete and submit reports to VAERS online at https://vaers.hhs.gov/reportevent.html. For further assistance with reporting to VAERS call 1-800-822-7967. The reports should include the words

"Pfizer-BioNTech COVID-19 Vaccine EUA" in the description section of the report.

5. The vaccination provider is responsible for responding to FDA requests for information about vaccine administration errors, adverse events, cases of MIS in adults and children, and cases of COVID-19 that result in hospitalization or death following administration of Pfizer-BioNTech COVID-19 Vaccine to recipients.

* Serious adverse events are defined as:
- Death;
- A life-threatening adverse event;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect;
- An important medical event that based on appropriate medical judgement may jeopardize the individual and may require medical or surgical intervention to prevent one of the outcomes listed above.

OTHER ADVERSE EVENT REPORTING TO VAERS AND PFIZER INC.

Vaccination providers may report to VAERS other adverse events that are not required to be reported using the contact information above.

To the extent feasible, report adverse events to Pfizer Inc. using the contact information below or by providing a copy of the VAERS form to Pfizer Inc.

Website	Fax number	Telephone number
www.pfizersafetyreporting.com	1-866-635-8337	1-800-438-1985

ADDITIONAL INFORMATION

For general questions, visit the website or call the telephone number provided below.

To access the most recent Pfizer-BioNTech COVID-19 Vaccine Fact Sheets, please scan the QR code provided below.

Global website	Telephone number
www.cvdvaccine.com 	1-877-829-2619 (1-877-VAX-CO19)

AVAILABLE ALTERNATIVES

There is no approved alternative vaccine to prevent COVID-19. There may be clinical trials or availability under EUA of other COVID-19 vaccines.

AUTHORITY FOR ISSUANCE OF THE EUA

The Secretary of Health and Human Services (HHS) has declared a public health emergency that justifies the emergency use of drugs and biological products during the COVID-19 pandemic. In response, FDA has issued an EUA for the unapproved product, Pfizer-BioNTech COVID-19 Vaccine, for active immunization against COVID-19 in individuals 16 years of age and older.

FDA issued this EUA, based on Pfizer-BioNTech's request and submitted data.

Although limited scientific information is available, based on the totality of the scientific evidence available to date, it is reasonable to believe that the Pfizer-BioNTech COVID-19 Vaccine may be effective for the prevention of COVID-19 in individuals as specified in the *Full EUA Prescribing Information*.

This EUA for the Pfizer-BioNTech COVID-19 Vaccine will end when the Secretary of HHS determines that the circumstances justifying the EUA no longer exist or when there is a change in the approval status of the product such that an EUA is no longer needed.

For additional information about Emergency Use Authorization visit FDA at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization.

The Countermeasures Injury Compensation Program

The Countermeasures Injury Compensation Program (CICP) is a federal program that has been created to help pay for related costs of medical care and other specific expenses to compensate people injured after use of certain medical countermeasures. Medical countermeasures are specific vaccines, medications, devices, or other items used to prevent, diagnose, or treat the public during a public health emergency or a security threat. For more information about CICP regarding the Pfizer-BioNTech COVID-19 Vaccine used to prevent COVID-19, visit www.hrsa.gov/cicp, email cicp@hrsa.gov, or call: 1-855-266-2427.

Manufactured by
Pfizer Inc., New York, NY 10017

BIONTECH
Manufactured for
BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

LAB-1450-3.0

Revised: December 2020

END SHORT VERSION FACT SHEET
Long Version (Full EUA Prescribing Information) Begins On Next Page

FULL EMERGENCY USE AUTHORIZATION (EUA) PRESCRIBING INFORMATION

PFIZER-BIONTECH COVID-19 VACCINE

FULL EMERGENCY USE AUTHORIZATION PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full emergency use authorization prescribing information are not listed.

FULL EMERGENCY USE AUTHORIZATION (EUA) PRESCRIBING INFORMATION

1 AUTHORIZED USE

Pfizer-BioNTech COVID-19 Vaccine is authorized for use under an Emergency Use Authorization (EUA) for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older.

2 DOSAGE AND ADMINISTRATION

For intramuscular injection only.

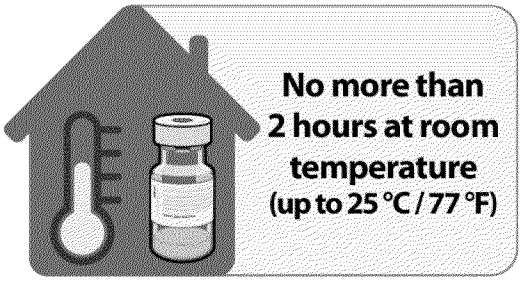
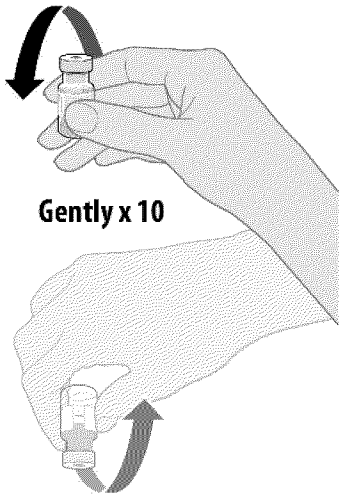
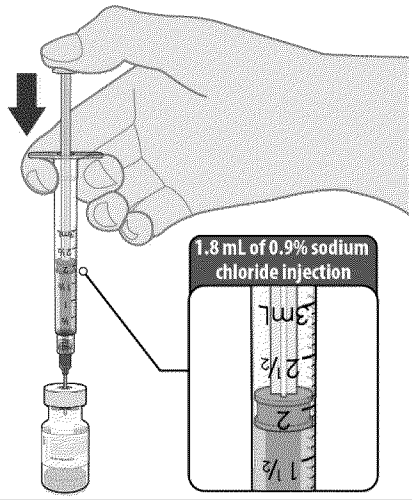
2.1 Preparation for Administration

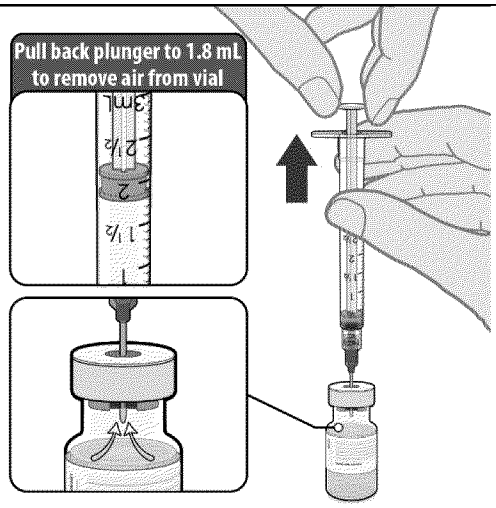
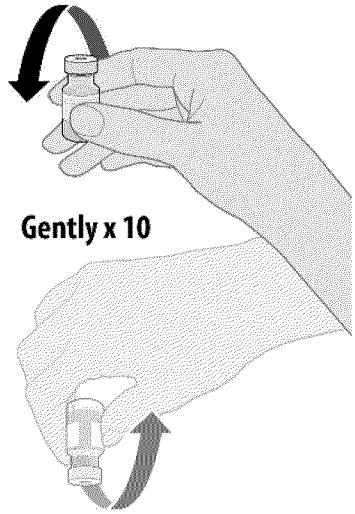
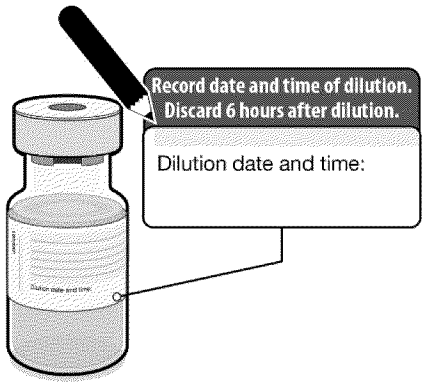
Prior to Dilution

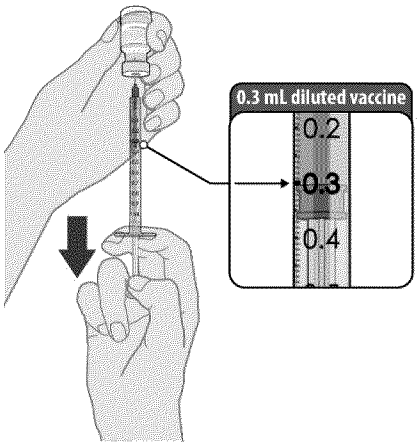
- The Pfizer-BioNTech COVID-19 Vaccine Multiple Dose Vial contains a volume of 0.45 mL, supplied as a frozen suspension that does not contain preservative. Each vial must be thawed and diluted prior to administration.
- Vials may be thawed in the refrigerator [2°C to 8°C (35°F to 46°F)] or at room temperature [up to 25°C (77°F)] *[see How Supplied/Storage and Handling (19)]*.
- Refer to thawing instructions in the panels below.

Dilution

- Dilute the vial contents using 1.8 mL of 0.9% Sodium Chloride Injection, USP (not provided) to form the Pfizer-BioNTech COVID-19 Vaccine. Do not use more than 1.8 mL of diluent.
- ONLY use 0.9% Sodium Chloride Injection, USP as the diluent. This diluent is not packaged with the vaccine and must be sourced separately. Do not use bacteriostatic 0.9% Sodium Chloride Injection or any other diluent.
- After dilution, one vial contains up to 6 doses of 0.3 mL. Vial labels and cartons may state that after dilution, a vial contains 5 doses of 0.3 mL. The information on the number of doses per vial after dilution in this Fact Sheet supersedes the number of doses stated on vial labels and cartons.
- Refer to dilution and dose preparation instructions in the panels below.

THAWING PRIOR TO DILUTION	
	• Thaw vial(s) of Pfizer-BioNTech COVID-19 Vaccine before use either by: o Allowing vial(s) to thaw in the refrigerator [2°C to 8°C (35°F to 46°F)]. A carton of vials may take up to 3 hours to thaw, and thawed vials can be stored in the refrigerator for up to five days (120 hours). o Allowing vial(s) to sit at room temperature [up to 25°C (77°F)] for 30 minutes. • Using either thawing method, vials must reach room temperature before dilution and must be diluted within 2 hours.
	• Before dilution invert vaccine vial gently 10 times. • Do not shake. • Inspect the liquid in the vial prior to dilution. The liquid is a white to off-white suspension and may contain white to off-white opaque amorphous particles. • Do not use if liquid is discolored or if other particles are observed.
DILUTION	
	• Obtain sterile 0.9% Sodium Chloride Injection, USP. Use only this as the diluent. • Using aseptic technique, withdraw 1.8 mL of diluent into a transfer syringe (21-gauge or narrower needle). • Cleanse the vaccine vial stopper with a single-use antiseptic swab. • Add 1.8 mL of 0.9% Sodium Chloride Injection, USP into the vaccine vial.

	• Equalize vial pressure before removing the needle from the vial by withdrawing 1.8 mL air into the empty diluent syringe.
	• Gently invert the vial containing the Pfizer-BioNTech COVID-19 Vaccine 10 times to mix. • Do not shake. • Inspect the vaccine in the vial. • The vaccine will be an off-white suspension. Do not use if vaccine is discolored or contains particulate matter.
	• Record the date and time of dilution on the Pfizer-BioNTech COVID-19 Vaccine vial label. • Store between 2°C to 25°C (35°F to 77°F). • Discard any unused vaccine 6 hours after dilution.

PREPARATION OF INDIVIDUAL 0.3 mL DOSES OF PFIZER-BIONTECH COVID-19 VACCINE	
	• Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab, and withdraw 0.3 mL of the Pfizer-BioNTech COVID-19 Vaccine preferentially using low dead-volume syringes and/or needles. • Administer immediately.

2.2 Administration Information

Visually inspect each dose in the dosing syringe prior to administration. The vaccine will be an off-white suspension. During the visual inspection,

- verify the final dosing volume of 0.3 mL.
- confirm there are no particulates and that no discoloration is observed.
- do not administer if vaccine is discolored or contains particulate matter.

Administer the Pfizer-BioNTech COVID-19 Vaccine intramuscularly.

After preparation, vials of Pfizer-BioNTech COVID-19 Vaccine contain up to six doses of 0.3 mL. Low dead-volume syringes and/or needles can be used to extract up to six 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.

2.3 Vaccination Schedule for Individuals 16 Years of Age and Older

The Pfizer-BioNTech COVID-19 Vaccine is administered intramuscularly as a series of two doses (0.3 mL each) three weeks apart.

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

3 DOSAGE FORMS AND STRENGTHS

Pfizer-BioNTech COVID-19 Vaccine is a suspension for injection. After preparation, a single dose is 0.3 mL.

4 CONTRAINDICATIONS

Do not administer Pfizer-BioNTech COVID-19 Vaccine to individuals with known history of a severe allergic reaction (e.g., anaphylaxis) to any component of the Pfizer-BioNTech COVID-19 Vaccine *[see Description (13)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Management of Acute Allergic Reactions

Appropriate medical treatment used to manage immediate allergic reactions must be immediately available in the event an acute anaphylactic reaction occurs following administration of Pfizer-BioNTech COVID-19 Vaccine.

Monitor Pfizer-BioNTech COVID-19 Vaccine recipients for the occurrence of immediate adverse reactions according to the Centers for Disease Control and Prevention guidelines (https://www.cdc.gov/vaccines/covid-19/).

5.2 Altered Immunocompetence

Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to the Pfizer-BioNTech COVID-19 Vaccine.

5.3 Limitation of Effectiveness

The Pfizer-BioNTech COVID-19 Vaccine may not protect all vaccine recipients.

6 OVERALL SAFETY SUMMARY

It is MANDATORY for vaccination providers to report to the Vaccine Adverse Event Reporting System (VAERS) all vaccine administration errors, all serious adverse events, cases of Multisystem Inflammatory Syndrome (MIS) in adults and children, and hospitalized or fatal cases of COVID-19 following vaccination with the Pfizer-BioNTech COVID-19 Vaccine. To the extent feasible, provide a copy of the VAERS form to Pfizer Inc. Please see the REQUIREMENTS AND INSTRUCTIONS FOR REPORTING ADVERSE EVENTS AND VACCINE ADMINISTRATION ERRORS section for details on reporting to VAERS and Pfizer Inc.

In clinical studies, adverse reactions in participants 16 years of age and older included pain at the injection site (84.1%), fatigue (62.9%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%), fever (14.2%), injection site swelling (10.5%), injection site redness (9.5%), nausea (1.1%), malaise (0.5%), and lymphadenopathy (0.3%).

Severe allergic reactions have been reported following the Pfizer-BioNTech COVID-19 Vaccine during mass vaccination outside of clinical trials.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of Pfizer-BioNTech COVID-19 Vaccine was evaluated in participants 16 years of age and older in two clinical studies conducted in the United States, Europe, Turkey, South Africa, and South America. Study BNT162-01 (Study 1) was a Phase 1/2, two-part, dose-escalation trial that enrolled 60 participants, 18 through 55 years of age. Study C4591001 (Study 2) is a Phase 1/2/3, multicenter, multinational, randomized, saline placebo-controlled, observer-blind, dose-finding, vaccine candidate-selection (Phase 1) and efficacy (Phase 2/3) study that has enrolled approximately 44,000 participants, 12 years of age or older. Of these, approximately 43,448 participants (21,720 Pfizer-BioNTech COVID-19 Vaccine; 21,728 placebo) in Phase 2/3 are 16 years of age or older (including 138 and 145 adolescents 16 and 17 years of age in the vaccine and placebo groups, respectively).

At the time of the analysis of Study 2 for the EUA, 37,586 (18,801 Pfizer-BioNTech COVID-19 Vaccine and 18,785 placebo) participants 16 years of age or older have been followed for a median of 2 months after the second dose of Pfizer-BioNTech COVID-19 Vaccine.

The safety evaluation in Study 2 is ongoing. The safety population includes participants enrolled by October 9, 2020, and includes safety data accrued through November 14, 2020. Participants 18 years and older in the reactogenicity subset are monitored for solicited local and systemic reactions and use of antipyretic medication after each vaccination in an electronic diary. Participants are being monitored for unsolicited adverse events, including serious adverse events, throughout the study [from Dose 1 through 1 month (all unsolicited adverse events) or 6 months (serious adverse events) after the last vaccination].

Demographic characteristics in Study 2 were generally similar with regard to age, gender, race, and ethnicity among participants who received Pfizer-BioNTech COVID-19 Vaccine and those who received placebo. Overall, among the total participants who received either the Pfizer-BioNTech COVID-19 Vaccine or placebo, 50.6% were male and 49.4% were female, 83.1% were White, 9.1% were Black or African American, 28.0% were Hispanic/Latino, 4.3% were Asian, and 0.5% were American Indian/Alaska Native.

Local and Systemic Adverse Reactions Solicited in the Study 2

Table 1 and Table 2 present the frequency and severity of solicited local and systemic reactions, respectively, within 7 days following each dose of Pfizer-BioNTech COVID-19 Vaccine and placebo in the subset of participants 18 to 55 years of age included in the EUA safety population who were monitored for reactogenicity with an electronic diary.

Table 3 and Table 4 present the frequency and severity of reported solicited local and systemic reactions, respectively, within 7 days of each dose of Pfizer-BioNTech COVID-19 Vaccine and placebo for participants 56 years of age and older.

Across both age groups, the mean duration of pain at the injection site after Dose 2 was 2.5 days (range 1 to 36 days), for redness 2.6 days (range 1 to 34 days), and for swelling 2.3 days (range 1 to 34 days) for participants in the Pfizer-BioNTech COVID-19 Vaccine group.

Solicited reactogenicity data in 16 and 17 year-old participants are limited.

Table 1: Study 2 – Frequency and Percentages of Participants with Solicited Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Participants 18-55 Years of Age‡ – Reactogenicity Subset of the Safety Population*

	Pfizer-BioNTech COVID-19 Vaccine Dose 1 N[a]=2291 n[b] (%)	Placebo Dose 1 N[a]=2298 n[b] (%)	Pfizer-BioNTech COVID-19 Vaccine Dose 2 N[a]=2098 n[b] (%)	Placebo Dose 2 N[a]=2103 n[b] (%)
Redness[c]				
Any (>2 cm)	104 (4.5)	26 (1.1)	123 (5.9)	14 (0.7)
Mild	70 (3.1)	16 (0.7)	73 (3.5)	8 (0.4)
Moderate	28 (1.2)	6 (0.3)	40 (1.9)	6 (0.3)
Severe	6 (0.3)	4 (0.2)	10 (0.5)	0 (0.0)
Swelling[c]				
Any (>2 cm)	132 (5.8)	11 (0.5)	132 (6.3)	5 (0.2)
Mild	88 (3.8)	3 (0.1)	80 (3.8)	3 (0.1)
Moderate	39 (1.7)	5 (0.2)	45 (2.1)	2 (0.1)
Severe	5 (0.2)	3 (0.1)	7 (0.3)	0 (0.0)
Pain at the injection site[d]				
Any	1904 (83.1)	322 (14.0)	1632 (77.8)	245 (11.7)
Mild	1170 (51.1)	308 (13.4)	1039 (49.5)	225 (10.7)
Moderate	710 (31.0)	12 (0.5)	568 (27.1)	20 (1.0)
Severe	24 (1.0)	2 (0.1)	25 (1.2)	0 (0.0)

Note: Reactions were collected in the electronic diary (e-diary) from Day 1 to Day 7 after vaccination.
a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.
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.
‡ Eight participants were between 16 and 17 years of age.
* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.

Table 2: Study 2 – Frequency and Percentages of Participants with Solicited Systemic Reactions, by Maximum Severity, Within 7 Days After Each Dose – Participants 18-55 Years of Age‡ – Safety Population*

	Pfizer-BioNTech COVID-19 Vaccine Dose 1 N[a]=2291 n[b] (%)	Placebo Dose 1 N[a]=2298 n[b] (%)	Pfizer-BioNTech COVID-19 Vaccine Dose 2 N[a]=2098 n[b] (%)	Placebo Dose 2 N[a]=2103 n[b] (%)
Fever				
≥38.0°C	85 (3.7)	20 (0.9)	331 (15.8)	10 (0.5)
≥38.0°C to 38.4°C	64 (2.8)	10 (0.4)	194 (9.2)	5 (0.2)
>38.4°C to 38.9°C	15 (0.7)	5 (0.2)	110 (5.2)	3 (0.1)
>38.9°C to 40.0°C	6 (0.3)	3 (0.1)	26 (1.2)	2 (0.1)
>40.0°C	0 (0.0)	2 (0.1)	1 (0.0)	0 (0.0)
Fatigue[c]				
Any	1085 (47.4)	767 (33.4)	1247 (59.4)	479 (22.8)
Mild	597 (26.1)	467 (20.3)	442 (21.1)	248 (11.8)
Moderate	455 (19.9)	289 (12.6)	708 (33.7)	217 (10.3)
Severe	33 (1.4)	11 (0.5)	97 (4.6)	14 (0.7)
Headache[c]				

	Pfizer-BioNTech COVID-19 Vaccine Dose 1 N[a]=2291 n[b] (%)	Placebo Dose 1 N[a]=2298 n[b] (%)	Pfizer-BioNTech COVID-19 Vaccine Dose 2 N[a]=2098 n[b] (%)	Placebo Dose 2 N[a]=2103 n[b] (%)
Any	959 (41.9)	775 (33.7)	1085 (51.7)	506 (24.1)
Mild	628 (27.4)	505 (22.0)	538 (25.6)	321 (15.3)
Moderate	308 (13.4)	251 (10.9)	480 (22.9)	170 (8.1)
Severe	23 (1.0)	19 (0.8)	67 (3.2)	15 (0.7)
Chills[c]				
Any	321 (14.0)	146 (6.4)	737 (35.1)	79 (3.8)
Mild	230 (10.0)	111 (4.8)	359 (17.1)	65 (3.1)
Moderate	82 (3.6)	33 (1.4)	333 (15.9)	14 (0.7)
Severe	9 (0.4)	2 (0.1)	45 (2.1)	0 (0.0)
Vomiting[d]				
Any	28 (1.2)	28 (1.2)	40 (1.9)	25 (1.2)
Mild	24 (1.0)	22 (1.0)	28 (1.3)	16 (0.8)
Moderate	4 (0.2)	5 (0.2)	8 (0.4)	9 (0.4)
Severe	0 (0.0)	1 (0.0)	4 (0.2)	0 (0.0)
Diarrhea[e]				
Any	255 (11.1)	270 (11.7)	219 (10.4)	177 (8.4)
Mild	206 (9.0)	217 (9.4)	179 (8.5)	144 (6.8)
Moderate	46 (2.0)	52 (2.3)	36 (1.7)	32 (1.5)
Severe	3 (0.1)	1 (0.0)	4 (0.2)	1 (0.0)
New or worsened muscle pain[c]				
Any	487 (21.3)	249 (10.8)	783 (37.3)	173 (8.2)
Mild	256 (11.2)	175 (7.6)	326 (15.5)	111 (5.3)
Moderate	218 (9.5)	72 (3.1)	410 (19.5)	59 (2.8)
Severe	13 (0.6)	2 (0.1)	47 (2.2)	3 (0.1)
New or worsened joint pain[c]				
Any	251 (11.0)	138 (6.0)	459 (21.9)	109 (5.2)
Mild	147 (6.4)	95 (4.1)	205 (9.8)	54 (2.6)
Moderate	99 (4.3)	43 (1.9)	234 (11.2)	51 (2.4)
Severe	5 (0.2)	0 (0.0)	20 (1.0)	4 (0.2)
Use of antipyretic or pain medication[f]	638 (27.8)	332 (14.4)	945 (45.0)	266 (12.6)

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

a. N = Number of participants reporting at least 1 yes or no response for the specified event after the specified dose.
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.
‡ Eight participants were between 16 and 17 years of age.
* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.

Table 3: Study 2 – Frequency and Percentages of Participants with Solicited Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Participants 56 Years of Age and Older – Safety Population*

	Pfizer-BioNTech COVID-19 Vaccine Dose 1 N[a]=1802 n[b] (%)	Placebo Dose 1 N[a]=1792 n[b] (%)	Pfizer-BioNTech COVID-19 Vaccine Dose 2 N[a]=1660 n[b] (%)	Placebo Dose 2 N[a]=1646 n[b] (%)
Redness[c]				
Any (>2 cm)	85 (4.7)	19 (1.1)	120 (7.2)	12 (0.7)
Mild	55 (3.1)	12 (0.7)	59 (3.6)	8 (0.5)
Moderate	27 (1.5)	5 (0.3)	53 (3.2)	3 (0.2)
Severe	3 (0.2)	2 (0.1)	8 (0.5)	1 (0.1)
Swelling[c]				
Any (>2 cm)	118 (6.5)	21 (1.2)	124 (7.5)	11 (0.7)
Mild	71 (3.9)	10 (0.6)	68 (4.1)	5 (0.3)
Moderate	45 (2.5)	11 (0.6)	53 (3.2)	5 (0.3)
Severe	2 (0.1)	0 (0.0)	3 (0.2)	1 (0.1)
Pain at the injection site[d]				
Any (>2 cm)	1282 (71.1)	166 (9.3)	1098 (66.1)	127 (7.7)
Mild	1008 (55.9)	160 (8.9)	792 (47.7)	125 (7.6)
Moderate	270 (15.0)	6 (0.3)	298 (18.0)	2 (0.1)
Severe	4 (0.2)	0 (0.0)	8 (0.5)	0 (0.0)

Note: Reactions were collected in the electronic diary (e-diary) from Day 1 to Day 7 after vaccination.
a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.
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.
* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.

Table 4: Study 2 – Frequency and Percentages of Participants with Solicited Systemic Reactions, by Maximum Severity, Within 7 Days After Each Dose – Participants 56 Years of Age and Older – Reactogenicity Subset of the Safety Population*

	Pfizer-BioNTech COVID-19 Vaccine Dose 1 N[a]=1802 n[b] (%)	Placebo Dose 1 N[a]=1792 n[b] (%)	Pfizer-BioNTech COVID-19 Vaccine Dose 2 N[a]=1660 n[b] (%)	Placebo Dose 2 N[a]=1646 n[b] (%)
Fever				
≥38.0°C	26 (1.4)	7 (0.4)	181 (10.9)	4 (0.2)
≥38.0°C to 38.4°C	23 (1.3)	2 (0.1)	131 (7.9)	2 (0.1)
>38.4°C to 38.9°C	1 (0.1)	3 (0.2)	45 (2.7)	1 (0.1)
>38.9°C to 40.0°C	1 (0.1)	2 (0.1)	5 (0.3)	1 (0.1)
>40.0°C	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue[c]				
Any	615 (34.1)	405 (22.6)	839 (50.5)	277 (16.8)
Mild	373 (20.7)	252 (14.1)	351 (21.1)	161 (9.8)
Moderate	240 (13.3)	150 (8.4)	442 (26.6)	114 (6.9)
Severe	2 (0.1)	3 (0.2)	46 (2.8)	2 (0.1)

	Pfizer-BioNTech COVID-19 Vaccine Dose 1 N[a]=1802 n[b] (%)	Placebo Dose 1 N[a]=1792 n[b] (%)	Pfizer-BioNTech COVID-19 Vaccine Dose 2 N[a]=1660 n[b] (%)	Placebo Dose 2 N[a]=1646 n[b] (%)
Headache[c]				
Any	454 (25.2)	325 (18.1)	647 (39.0)	229 (13.9)
Mild	348 (19.3)	242 (13.5)	422 (25.4)	165 (10.0)
Moderate	104 (5.8)	80 (4.5)	216 (13.0)	60 (3.6)
Severe	2 (0.1)	3 (0.2)	9 (0.5)	4 (0.2)
Chills[c]				
Any	113 (6.3)	57 (3.2)	377 (22.7)	46 (2.8)
Mild	87 (4.8)	40 (2.2)	199 (12.0)	35 (2.1)
Moderate	26 (1.4)	16 (0.9)	161 (9.7)	11 (0.7)
Severe	0 (0.0)	1 (0.1)	17 (1.0)	0 (0.0)
Vomiting[d]				
Any	9 (0.5)	9 (0.5)	11 (0.7)	5 (0.3)
Mild	8 (0.4)	9 (0.5)	9 (0.5)	5 (0.3)
Moderate	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)
Severe	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Diarrhea[e]				
Any	147 (8.2)	118 (6.6)	137 (8.3)	99 (6.0)
Mild	118 (6.5)	100 (5.6)	114 (6.9)	73 (4.4)
Moderate	26 (1.4)	17 (0.9)	21 (1.3)	22 (1.3)
Severe	3 (0.2)	1 (0.1)	2 (0.1)	4 (0.2)
New or worsened muscle pain[c]				
Any	251 (13.9)	149 (8.3)	477 (28.7)	87 (5.3)
Mild	168 (9.3)	100 (5.6)	202 (12.2)	57 (3.5)
Moderate	82 (4.6)	46 (2.6)	259 (15.6)	29 (1.8)
Severe	1 (0.1)	3 (0.2)	16 (1.0)	1 (0.1)
New or worsened joint pain[c]				
Any	155 (8.6)	109 (6.1)	313 (18.9)	61 (3.7)
Mild	101 (5.6)	68 (3.8)	161 (9.7)	35 (2.1)
Moderate	52 (2.9)	40 (2.2)	145 (8.7)	25 (1.5)
Severe	2 (0.1)	1 (0.1)	7 (0.4)	1 (0.1)
Use of antipyretic or pain medication	358 (19.9)	213 (11.9)	625 (37.7)	161 (9.8)

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

a. N = Number of participants reporting at least 1 yes or no response for the specified event after the specified dose.
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.
* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.

Unsolicited Adverse Events

Serious Adverse Events

In Study 2, among participants 16 to 55 years of age who had received at least 1 dose of vaccine or placebo (Pfizer-BioNTech COVID-19 Vaccine = 10,841; placebo = 10,851), serious adverse events from Dose 1 through up to 30 days after Dose 2 in ongoing follow-up were reported by 0.4% of Pfizer-BioNTech COVID-19 Vaccine recipients and by 0.3% of placebo recipients. In a similar analysis, in participants 56 years of age and older (Pfizer-BioNTech COVID-19 Vaccine = 7960, placebo = 7934), serious adverse events were reported by 0.8% of Pfizer-BioNTech COVID-19 Vaccine recipients and by 0.6% of placebo recipients who received at least 1 dose of Pfizer-BioNTech COVID-19 Vaccine or placebo, respectively. In these analyses, 91.6% of study participants had at least 30 days of follow-up after Dose 2. Appendicitis was reported as a serious adverse event for 12 participants, and numerically higher in the vaccine group, 8 vaccine participants and 4 placebo participants. Currently available information is insufficient to determine a causal relationship with the vaccine. There were no other notable patterns or numerical imbalances between treatment groups for specific categories of serious adverse events (including neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to Pfizer-BioNTech COVID-19 Vaccine.

Non-Serious Adverse Events

Overall in Study 2 in which 10,841 participants 16 to 55 years of age received Pfizer-BioNTech COVID-19 Vaccine and 10,851 participants received placebo, non-serious adverse events from Dose 1 through up to 30 days after Dose 2 in ongoing follow-up were reported in 29.3% of participants who received Pfizer-BioNTech COVID-19 Vaccine and 13.2% of participants in the placebo group, for participants who received at least 1 dose. Overall in a similar analysis in which 7960 participants 56 years of age and older received Pfizer-BioNTech COVID-19 Vaccine, non-serious adverse events within 30 days were reported in 23.8% of participants who received Pfizer-BioNTech COVID-19 Vaccine and 11.7% of participants in the placebo group, for participants who received at least 1 dose. In these analyses, 91.6% of study participants had at least 30 days of follow-up after Dose 2. The higher frequency of reported unsolicited non-serious adverse events among Pfizer BioNTech COVID-19 Vaccine recipients compared to placebo recipients was primarily attributed to local and systemic adverse events reported during the first 7 days following vaccination that are consistent with adverse reactions solicited among participants in the reactogenicity subset and presented in Tables 3 and 4. From Dose 1 through 30 days after Dose 2, reports of lymphadenopathy were imbalanced with notably more cases in the Pfizer-BioNTech COVID-19 Vaccine group (64) vs. the placebo group (6), which is plausibly related to vaccination. Throughout the safety follow-up period to date, Bell's palsy (facial paralysis) was reported by four participants in the Pfizer-BioNTech COVID-19 Vaccine group. Onset of facial paralysis was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of Bell's palsy were reported in the placebo group. Currently available information is insufficient to determine a causal relationship with the vaccine. There were no other notable patterns or numerical imbalances between treatment groups for specific categories of non-serious adverse events (including other neurologic or neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to Pfizer-BioNTech COVID-19 Vaccine.

8 REQUIREMENTS AND INSTRUCTIONS FOR REPORTING ADVERSE EVENTS AND VACCINE ADMINISTRATION ERRORS

See Overall Safety Summary (Section 6) for additional information.

The vaccination provider enrolled in the federal COVID-19 Vaccination Program is responsible for MANDATORY reporting of the listed events following Pfizer-BioNTech COVID-19 Vaccine to the Vaccine Adverse Event Reporting System (VAERS):

- Vaccine administration errors whether or not associated with an adverse event
- Serious adverse events* (irrespective of attribution to vaccination)
- Cases of Multisystem Inflammatory Syndrome (MIS) in children and adults
- Cases of COVID-19 that result in hospitalization or death

*Serious adverse events are defined as:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- An important medical event that based on appropriate medical judgement may jeopardize the individual and may require medical or surgical intervention to prevent one of the outcomes listed above

Instructions for Reporting to VAERS

The vaccination provider enrolled in the federal COVID-19 Vaccination Program should complete and submit a VAERS form to FDA using one of the following methods:

- Complete and submit the report online: https://vaers.hhs.gov/reportevent.html, or
- If you are unable to submit this form electronically, you may fax it to VAERS at 1-877-721-0366. If you need additional help submitting a report you may call the VAERS toll-free information line at 1-800-822-7967 or send an email to info@vaers.org.

IMPORTANT: When reporting adverse events or vaccine administration errors to VAERS, please complete the entire form with detailed information. It is important that the information reported to FDA be as detailed and complete as possible. Information to include:

- Patient demographics (e.g., patient name, date of birth)
- Pertinent medical history
- Pertinent details regarding admission and course of illness
- Concomitant medications
- Timing of adverse event(s) in relationship to administration of the Pfizer-BioNTech COVID-19 Vaccine
- Pertinent laboratory and virology information
- Outcome of the event and any additional follow-up information if it is available at the time of the VAERS report. Subsequent reporting of follow-up information should be completed if additional details become available.

The following steps are highlighted to provide the necessary information for safety tracking:

1. In Box 17, provide information on Pfizer-BioNTech COVID-19 Vaccine and any other vaccines administered on the same day; and in Box 22, provide information on any other vaccines received within one month prior.
2. In Box 18, description of the event:
    a. Write "Pfizer-BioNTech COVID-19 Vaccine EUA" as the first line.
    b. Provide a detailed report of vaccine administration error and/or adverse event. It is important to provide detailed information regarding the patient and adverse event/medication error for ongoing safety evaluation of this unapproved vaccine. Please see information to include listed above.

3. Contact information:
    a. In Box 13, provide the name and contact information of the prescribing healthcare provider or institutional designee who is responsible for the report.
    b. In Box 14, provide the name and contact information of the best doctor/healthcare professional to contact about the adverse event.
    c. In Box 15, provide the address of the facility where vaccine was given (NOT the healthcare provider's office address).

Other Reporting Instructions

Vaccination providers may report to VAERS other adverse events that are not required to be reported using the contact information above.

To the extent feasible, report adverse events to Pfizer Inc. using the contact information below or by providing a copy of the VAERS form to Pfizer Inc.

Website	Fax number	Telephone number
www.pfizersafetyreporting.com	1-866-635-8337	1-800-438-1985

10 DRUG INTERACTIONS

There are no data to assess the concomitant administration of the Pfizer-BioNTech COVID-19 Vaccine with other vaccines.

11 USE IN SPECIFIC POPULATIONS

11.1 Pregnancy

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Available data on Pfizer-BioNTech COVID-19 Vaccine administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

11.2 Lactation

Risk Summary

Data are not available to assess the effects of Pfizer-BioNTech COVID-19 Vaccine on the breastfed infant or on milk production/excretion.

11.3 Pediatric Use

Emergency Use Authorization of Pfizer-BioNTech COVID-19 Vaccine in adolescents 16 and 17 years of age is based on extrapolation of safety and effectiveness from adults 18 years of age and older. Emergency Use Authorization of Pfizer BioNTech COVID-19 Vaccine does not include use in individuals younger than 16 years of age.

11.4 Geriatric Use

Clinical studies of Pfizer-BioNTech COVID-19 Vaccine include participants 65 years of age and older and their data contributes to the overall assessment of safety and efficacy *[see Overall Safety Summary (6.1) and Clinical Trial Results and Supporting Data for EUA (18.1)]*. Of the total number of Pfizer-BioNTech COVID-19 Vaccine recipients in Study 2 (N=20,033), 21.4% (n=4,294) were 65 years of age and older and 4.3% (n=860) were 75 years of age and older.

13 DESCRIPTION

The Pfizer-BioNTech COVID-19 Vaccine is supplied as a frozen suspension in multiple dose vials; each vial must be diluted with 1.8 mL of sterile 0.9% Sodium Chloride Injection, USP prior to use to form the vaccine. Each dose of the Pfizer-BioNTech COVID-19 Vaccine contains 30 mcg of a nucleoside-modified messenger RNA (modRNA) encoding the viral spike (S) glycoprotein of SARS-CoV-2.

Each dose of the Pfizer-BioNTech COVID-19 Vaccine also includes the following ingredients: lipids (0.43 mg (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 0.05 mg 2[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 0.09 mg 1,2-distearoyl-sn-glycero-3-phosphocholine, and 0.2 mg cholesterol), 0.01 mg potassium chloride, 0.01 mg monobasic potassium phosphate, 0.36 mg sodium chloride, 0.07 mg dibasic sodium phosphate dihydrate, and 6 mg sucrose. The diluent (0.9% Sodium Chloride Injection, USP) contributes an additional 2.16 mg sodium chloride per dose.

The Pfizer-BioNTech COVID-19 Vaccine does not contain preservative. The vial stoppers are not made with natural rubber latex.

14 CLINICAL PHARMACOLOGY

14.1 Mechanism of Action

The modRNA in the Pfizer-BioNTech COVID-19 Vaccine is formulated in lipid particles, which enable delivery of the RNA into host cells to allow expression of the SARS-CoV-2 S antigen. The vaccine elicits an immune response to the S antigen, which protects against COVID-19.

18 CLINICAL TRIAL RESULTS AND SUPPORTING DATA FOR EUA

18.1 Efficacy in Participants 16 Years of Age and Older

Study 2 is a multicenter, multinational, Phase 1/2/3, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate–selection, and efficacy study in participants 12 years of age and older. Randomization was stratified by age: 12 through 15 years of age, 16 through 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥56-year stratum. The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19. Participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, were included as were participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV).

In the Phase 2/3 portion approximately 44,000 participants 12 years of age and older were randomized equally and received 2 doses of Pfizer-BioNTech COVID-19 Vaccine or placebo separated by 21 days. Participants are planned to be followed for up to 24 months, for assessments of safety and efficacy against COVID-19.

The population for the analysis of the primary efficacy endpoint included, 36,621 participants 12 years of age and older (18,242 in the Pfizer-BioNTech COVID-19 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. Table 5 presents the specific demographic characteristics in the studied population.

Table 5: Demographics (population for the primary efficacy endpoint)[a]

	Pfizer-BioNTech COVID-19 Vaccine (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 through 15 years	46 (0.3)	42 (0.2)
≥16 through 17 years	66 (0.4)	68 (0.4)
≥16 through 64 years	14,216 (77.9)	14,299 (77.8)
≥65 through 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 disease
   - 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)

Efficacy Against COVID-19

The population in the primary efficacy analysis included all participants 12 years of age and older who had been enrolled from July 27, 2020, and followed for the development of COVID-19 through November 14, 2020. Participants 18 to 55 years of age and 56 years of age and older began enrollment from July 27,2020, 16 to 17 years of age began enrollment from September 16, 2020 and 12 to 15 years of age began enrollment from October 15, 2020.

The 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

First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection*			
Subgroup	**Pfizer-BioNTech COVID-19 Vaccine 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 subjects[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 and older	1 0.508 (3848)	19 0.511 (3880)	94.7 (66.7, 99.9)[g]
First COVID-19 occurrence from 7 days after Dose 2 in participants with or without evidence of prior SARS-CoV-2 infection			
Subgroup	**Pfizer-BioNTech COVID-19 Vaccine 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 subjects[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 and older	1 0.530 (4044)	19 0.532 (4067)	94.7 (66.8, 99.9)[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).

* 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 participants 12 to 15 years of age.
f. Credible interval for VE was calculated using a beta-binomial model with a beta (0.700102, 1) prior for θ=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. Confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.

19 HOW SUPPLIED/STORAGE AND HANDLING

Pfizer-BioNTech COVID-19 Vaccine Suspension for Intramuscular Injection, Multiple Dose Vials are supplied in a carton containing 25 multiple dose vials (NDC 59267-1000-3) or 195 multiple dose vials (NDC 59267-1000-2). After dilution, one vial contains up to 6 doses of 0.3 mL. Vial labels and cartons may state that after dilution, a vial contains 5 doses of 0.3 mL. The information on the number of doses per vial after dilution in this Fact Sheet supersedes the number of doses stated on vial labels and cartons.

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

Do not refreeze thawed vials.

Frozen Vials Prior to Use

Cartons of Pfizer-BioNTech COVID-19 Vaccine Multiple Dose Vials arrive in thermal containers with dry ice. Once received, remove the vial cartons immediately from the thermal container and store in an ultra-low temperature freezer between -80°C to -60°C (-112°F to -76°F). Vials must be kept frozen between -80°C to -60°C (-112°F to -76°F) and protected from light, in the original cartons, until ready to use.

If an ultra-low temperature freezer is not available, the thermal container in which the Pfizer-BioNTech COVID-19 Vaccine arrives may be used as temporary storage when consistently re-filled to the top of the container with dry ice. Refer to the re-icing guidelines packed in the original thermal container for instructions regarding the use of the thermal container for temporary storage. The thermal container maintains a temperature range of -90°C to -60°C (-130°F to -76°F). Storage within this temperature range is not considered an excursion from the recommended storage condition.

Thawed Vials Before Dilution

Thawed Under Refrigeration
Thaw and then store undiluted vials in the refrigerator [2°C to 8°C (35°F to 46°F)] for up to 5 days (120 hours). A carton of 25 vials or 195 vials may take up to 2 or 3 hours, respectively, to thaw in the refrigerator, whereas a fewer number of vials will thaw in less time.

Thawed at Room Temperature
For immediate use, thaw undiluted vials at room temperature [up to 25°C (77°F)] for 30 minutes. Thawed vials can be handled in room light conditions.

Vials must reach room temperature before dilution.

Undiluted vials may be stored at room temperature for no more than 2 hours.

Vials After Dilution

After dilution, store vials between 2°C to 25°C (35°F to 77°F) and use within 6 hours from the time of dilution. During storage, minimize exposure to room light, and avoid exposure to direct sunlight and ultraviolet light. Any vaccine remaining in vials must be discarded after 6 hours. Do not refreeze.

20 PATIENT COUNSELING INFORMATION

Advise the recipient or caregiver to read the Fact Sheet for Recipients and Caregivers.

The vaccination provider must include vaccination information in the state/local jurisdiction's Immunization Information System (IIS) or other designated system. Advise recipient or caregiver that more information about IISs can be found at: https://www.cdc.gov/vaccines/programs/iis/about.html.

21 CONTACT INFORMATION

For general questions, visit the website or call the telephone number provided below.

Website	Telephone number
www.cvdvaccine.com	1-877-829-2619 (1-877-VAX-CO19)

This Full EUA Prescribing Information may have been updated. For the most recent Full EUA Prescribing Information, please see www.cvdvaccine.com.

Manufactured by
Pfizer Inc., New York, NY 10017

Manufactured for
BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

LAB-1457-3.0

Revised: December 2020

FACT SHEET FOR HEALTHCARE PROVIDERS ADMINISTERING VACCINE (VACCINATION PROVIDERS)

EMERGENCY USE AUTHORIZATION (EUA) OF THE PFIZER-BIONTECH COVID-19 VACCINE TO PREVENT CORONAVIRUS DISEASE 2019 (COVID-19)

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product, **Pfizer-BioNTech COVID-19 Vaccine**, for active immunization to prevent COVID-19 in individuals 16 years of age and older.

SUMMARY OF INSTRUCTIONS FOR COVID-19 VACCINATION PROVIDERS

Vaccination providers enrolled in the federal COVID-19 Vaccination Program must report all vaccine administration errors, all serious adverse events, cases of Multisystem Inflammatory Syndrome (MIS) in adults and children, and cases of COVID-19 that result in hospitalization or death following administration of Pfizer-BioNTech COVID-19 Vaccine. See "MANDATORY REQUIREMENTS FOR PFIZER-BIONTECH COVID-19 VACCINE ADMINISTRATION UNDER EMERGENCY USE AUTHORIZATION" for reporting requirements.

The Pfizer-BioNTech COVID-19 Vaccine is a suspension for intramuscular injection administered as a series of two doses (0.3 mL each) 3 weeks apart.

See this Fact Sheet for instructions for preparation and administration. This Fact Sheet may have been updated. For the most recent Fact Sheet, please see www.cvdvaccine.com.

For information on clinical trials that are testing the use of the Pfizer-BioNTech COVID-19 Vaccine for active immunization against COVID-19, please see www.clinicaltrials.gov.

DESCRIPTION OF COVID-19

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the novel coronavirus, SARS-CoV-2, that appeared in late 2019. It is predominantly a respiratory illness that can affect other organs. People with COVID-19 have reported a wide range of symptoms, ranging from mild symptoms to severe illness. Symptoms may appear 2 to 14 days after exposure to the virus. Symptoms may include: fever or chills; cough; shortness of breath; fatigue; muscle or body aches; headache; new loss of taste or smell; sore throat; congestion or runny nose; nausea or vomiting; diarrhea.

DOSAGE AND ADMINISTRATION

Storage and Handling

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

Do not refreeze thawed vials.

Frozen Vials Prior to Use

Cartons of Pfizer-BioNTech COVID-19 Vaccine Multiple Dose Vials arrive in thermal containers with dry ice. Once received, remove the vial cartons immediately from the thermal container and store in an ultra-low temperature freezer between -80°C to -60°C (-112°F to -76°F). Vials must be kept frozen between -80°C to -60°C (-112°F to -76°F) and protected from light until ready to use.

If an ultra-low temperature freezer is not available, the thermal container in which the Pfizer-BioNTech COVID-19 Vaccine arrives may be used as temporary storage when consistently re-filled to the top of the container with dry ice. Refer to the re-icing guidelines packed in the original thermal container for instructions regarding the use of the thermal container for temporary storage. The thermal container maintains a temperature range of -90°C to -60°C (-130°F to -76°F). Storage within this temperature range is not considered an excursion from the recommended storage condition.

Thawed Vials Before Dilution

Thawed Under Refrigeration
Thaw and then store undiluted vials in the refrigerator [2°C to 8°C (35°F to 46°F)] for up to 5 days (120 hours). A carton of 25 vials or 195 vials may take up to 2 or 3 hours, respectively, to thaw in the refrigerator, whereas a fewer number of vials will thaw in less time.

Thawed at Room Temperature
For immediate use, thaw undiluted vials at room temperature [up to 25°C (77°F)] for 30 minutes. Thawed vials can be handled in room light conditions. Vials must reach room temperature before dilution.

Undiluted vials may be stored at room temperature for no more than 2 hours.

Vials After Dilution

- After dilution, store vials between 2°C to 25°C (35°F to 77°F) and use within 6 hours from the time of dilution.
- During storage, minimize exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.
- Any vaccine remaining in vials must be discarded after 6 hours.
- Do not refreeze.

Dosing and Schedule

The Pfizer-BioNTech COVID-19 Vaccine is administered intramuscularly as a series of two doses (0.3 mL each) 3 weeks apart.

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

Dose Preparation

Prior to Dilution

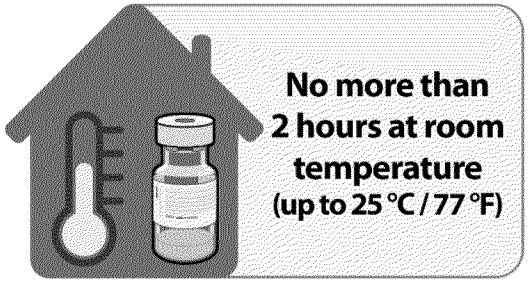
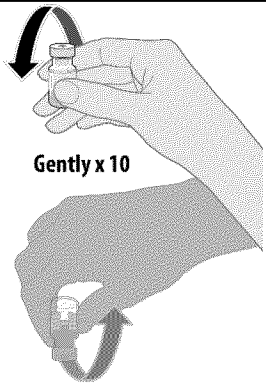
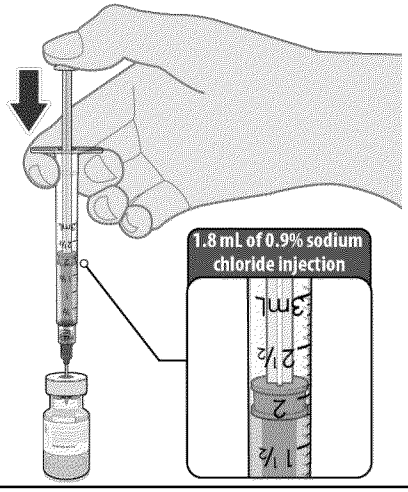
- The Pfizer-BioNTech COVID-19 Vaccine Multiple Dose Vial contains a volume of 0.45 mL, supplied as a frozen suspension that does not contain preservative. Each vial must be thawed and diluted prior to administration.
- Vials may be thawed in the refrigerator [2°C to 8°C (35°F to 46°F)] or at room temperature [up to 25°C (77°F)] *(see Storage and Handling)*.
- Refer to thawing instructions in the panels below.

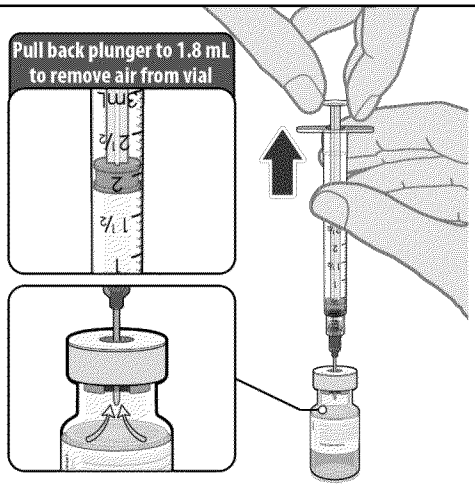
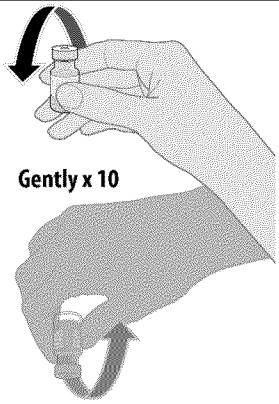
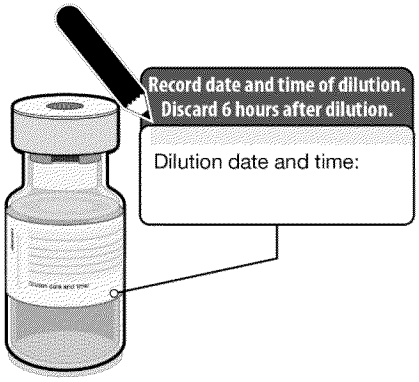
Dilution

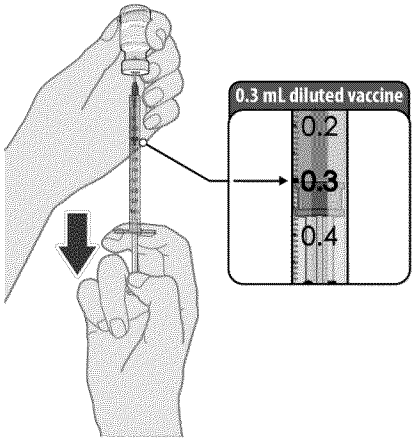
Dilute the vial contents using 1.8 mL of 0.9% Sodium Chloride Injection, USP (not provided) to form the Pfizer-BioNTech COVID-19 Vaccine. ONLY use 0.9% Sodium Chloride Injection, USP as the diluent. This diluent is not packaged with the vaccine and must be sourced separately. Do not use bacteriostatic 0.9% Sodium Chloride Injection or any other diluent. Do not add more than 1.8 mL of diluent.

After dilution, one vial contains 6 doses of 0.3 mL. Vial labels and cartons may state that after dilution, a vial contains 5 doses of 0.3 mL. The information in this Fact Sheet regarding the number of doses per vial after dilution supersedes the number of doses stated on vial labels and cartons.

- Refer to dilution and dose preparation instructions in the panels below.

THAWING PRIOR TO DILUTION	
	• Thaw vial(s) of Pfizer-BioNTech COVID-19 Vaccine before use either by: ○ Allowing vial(s) to thaw in the refrigerator [2ºC to 8ºC (35ºF to 46ºF)]. A carton of vials may take up to 3 hours to thaw, and thawed vials can be stored in the refrigerator for up to five days (120 hours). ○ Allowing vial(s) to sit at room temperature [up to 25ºC (77ºF)] for 30 minutes. • Using either thawing method, vials must reach room temperature before dilution and must be diluted within 2 hours.
	• Before dilution invert vaccine vial gently 10 times. • Do not shake. • Inspect the liquid in the vial prior to dilution. The liquid is a white to off-white suspension and may contain white to off-white opaque amorphous particles. • Do not use if liquid is discolored or if other particles are observed.
DILUTION	
	• Obtain sterile 0.9% Sodium Chloride Injection, USP. Use only this as the diluent. • Using aseptic technique, withdraw 1.8 mL of diluent into a transfer syringe (21-gauge or narrower needle). • Cleanse the vaccine vial stopper with a single-use antiseptic swab. • Add 1.8 mL of 0.9% Sodium Chloride Injection, USP into the vaccine vial.

	• Equalize vial pressure before removing the needle from the vial by withdrawing 1.8 mL air into the empty diluent syringe.
	• Gently invert the vial containing the Pfizer-BioNTech COVID-19 Vaccine 10 times to mix. • Do not shake. • Inspect the vaccine in the vial. • The vaccine will be an off-white suspension. Do not use if vaccine is discolored or contains particulate matter.
	• Record the date and time of dilution on the Pfizer-BioNTech COVID-19 Vaccine vial label. • Store between 2°C to 25°C (35°F to 77°F). • Discard any unused vaccine 6 hours after dilution.

PREPARATION OF INDIVIDUAL 0.3 mL DOSES OF PFIZER-BIONTECH COVID-19 VACCINE	
	• Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab, and withdraw 0.3 mL of the Pfizer-BioNTech COVID-19 Vaccine preferentially using a low dead-volume syringe and/or 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. • Administer immediately.

Administration

Visually inspect each dose in the dosing syringe prior to administration. The vaccine will be an off-white suspension. During the visual inspection,

- verify the final dosing volume of 0.3 mL.
- confirm there are no particulates and that no discoloration is observed.
- do not administer if vaccine is discolored or contains particulate matter.

Administer the Pfizer-BioNTech COVID-19 Vaccine intramuscularly.

After dilution, vials of Pfizer-BioNTech COVID-19 Vaccine contain six doses of 0.3mL of vaccine. Low dead-volume syringes and/or needles can be used to extract six 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 content.
- Do not pool excess vaccine from multiple vials.

Contraindications

Do not administer Pfizer-BioNTech COVID-19 Vaccine to individuals with known history of a severe allergic reaction (e.g., anaphylaxis) to any component of the Pfizer-BioNTech COVID-19 Vaccine *(see Full EUA Prescribing Information)*.

Warnings

Appropriate medical treatment used to manage immediate allergic reactions must be immediately available in the event an acute anaphylactic reaction occurs

following administration of Pfizer-BioNTech COVID-19 Vaccine.

Monitor Pfizer-BioNTech COVID-19 Vaccine recipients for the occurrence of immediate adverse reactions according to the Centers for Disease Control and Prevention guidelines (https://www.cdc.gov/vaccines/covid-19/).

Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to the Pfizer-BioNTech COVID-19 Vaccine.

Pfizer-BioNTech COVID-19 Vaccine may not protect all vaccine recipients.

Adverse Reactions

Adverse reactions following the Pfizer-BioNTech COVID-19 Vaccine that have been reported in clinical trials include injection site pain, fatigue, headache, muscle pain, chills, joint pain, fever, injection site swelling, injection site redness, nausea, malaise, and lymphadenopathy *(see Full EUA Prescribing Information)*.

Severe allergic reactions have been reported following the Pfizer-BioNTech COVID-19 Vaccine during mass vaccination outside of clinical trials.

Additional adverse reactions, some of which may be serious, may become apparent with more widespread use of the Pfizer-BioNTech COVID-19 Vaccine.

Use with Other Vaccines

There is no information on the co-administration of the Pfizer-BioNTech COVID-19 Vaccine with other vaccines.

INFORMATION TO PROVIDE TO VACCINE RECIPIENTS/CAREGIVERS

As the vaccination provider, you must communicate to the recipient or their caregiver, information consistent with the "Fact Sheet for Recipients and Caregivers" (and provide a copy or direct the individual to the website www.cvdvaccine.com to obtain the Fact Sheet) prior to the individual receiving Pfizer-BioNTech COVID-19 Vaccine, including:

- FDA has authorized the emergency use of the Pfizer-BioNTech COVID-19 Vaccine, which is not an FDA-approved vaccine.
- The recipient or their caregiver has the option to accept or refuse Pfizer-BioNTech COVID-19 Vaccine.
- The significant known and potential risks and benefits of Pfizer-BioNTech COVID-19 Vaccine, and the extent to which such risks and benefits are unknown.
- Information about available alternative vaccines and the risks and benefits of those alternatives.

For information on clinical trials that are testing the use of the Pfizer-BioNTech COVID-19 Vaccine to prevent COVID-19, please see www.clinicaltrials.gov.

Provide a vaccination card to the recipient or their caregiver with the date when the recipient needs to return for the second dose of Pfizer-BioNTech COVID-19 Vaccine.

Provide the v-safe information sheet to vaccine recipients/caregivers and encourage vaccine recipients to participate in v-safe. V-safe is a new voluntary smartphone-based tool that uses text messaging and web surveys to check in with people who have been vaccinated to identify potential side effects after COVID-19 vaccination. V-safe asks questions that help CDC monitor the safety of COVID-19 vaccines. V-safe also provides second-dose reminders if needed and live telephone follow-up by CDC if participants report a significant health impact following COVID-19 vaccination. For more information, visit: www.cdc.gov/vsafe.

MANDATORY REQUIREMENTS FOR PFIZER-BIONTECH COVID-19 VACCINE ADMINISTRATION UNDER EMERGENCY USE AUTHORIZATION

In order to mitigate the risks of using this unapproved product under EUA and to optimize the potential benefit of Pfizer-BioNTech COVID-19 Vaccine, the following items are required. Use of unapproved Pfizer-BioNTech COVID-19 Vaccine for active immunization to prevent COVID-19 under this EUA is limited to the following (all requirements **must** be met):

1. Pfizer-BioNTech COVID-19 Vaccine is authorized for use in individuals 16 years of age and older.

2. The vaccination provider must communicate to the individual receiving the Pfizer-BioNTech COVID-19 Vaccine or their caregiver, information consistent with the "Fact Sheet for Recipients and Caregivers" prior to the individual receiving Pfizer-BioNTech COVID-19 Vaccine.

3. The vaccination provider must include vaccination information in the state/local jurisdiction's Immunization Information System (IIS) or other designated system.

4. The vaccination provider is responsible for mandatory reporting of the following to the Vaccine Adverse Event Reporting System (VAERS):
    - vaccine administration errors whether or not associated with an adverse event,
    - serious adverse events* (irrespective of attribution to vaccination),
    - cases of Multisystem Inflammatory Syndrome (MIS) in adults and children, and
    - cases of COVID-19 that result in hospitalization or death.

    Complete and submit reports to VAERS online at https://vaers.hhs.gov/reportevent.html. For further assistance with reporting

to VAERS call 1-800-822-7967. The reports should include the words "Pfizer-BioNTech COVID-19 Vaccine EUA" in the description section of the report.

5. The vaccination provider is responsible for responding to FDA requests for information about vaccine administration errors, adverse events, cases of MIS in adults and children, and cases of COVID-19 that result in hospitalization or death following administration of Pfizer-BioNTech COVID-19 Vaccine to recipients.

* Serious adverse events are defined as:
- Death;
- A life-threatening adverse event;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect;
- An important medical event that based on appropriate medical judgement may jeopardize the individual and may require medical or surgical intervention to prevent one of the outcomes listed above.

OTHER ADVERSE EVENT REPORTING TO VAERS AND PFIZER INC.

Vaccination providers may report to VAERS other adverse events that are not required to be reported using the contact information above.

To the extent feasible, report adverse events to Pfizer Inc. using the contact information below or by providing a copy of the VAERS form to Pfizer Inc.

Website	Fax number	Telephone number
www.pfizersafetyreporting.com	1-866-635-8337	1-800-438-1985

ADDITIONAL INFORMATION

For general questions, visit the website or call the telephone number provided below.

To access the most recent Pfizer-BioNTech COVID-19 Vaccine Fact Sheets, please scan the QR code provided below.

Global website	Telephone number
www.cvdvaccine.com 	1-877-829-2619 (1-877-VAX-CO19)

AVAILABLE ALTERNATIVES

There is no approved alternative vaccine to prevent COVID-19. There may be clinical trials or availability under EUA of other COVID-19 vaccines.

AUTHORITY FOR ISSUANCE OF THE EUA

The Secretary of Health and Human Services (HHS) has declared a public health emergency that justifies the emergency use of drugs and biological products during the COVID-19 pandemic. In response, FDA has issued an EUA for the unapproved product, Pfizer-BioNTech COVID-19 Vaccine, for active immunization against COVID-19 in individuals 16 years of age and older.

FDA issued this EUA, based on Pfizer-BioNTech's request and submitted data.

Although limited scientific information is available, based on the totality of the scientific evidence available to date, it is reasonable to believe that the Pfizer-BioNTech COVID-19 Vaccine may be effective for the prevention of COVID-19 in individuals as specified in the *Full EUA Prescribing Information*.

This EUA for the Pfizer-BioNTech COVID-19 Vaccine will end when the Secretary of HHS determines that the circumstances justifying the EUA no longer exist or when there is a change in the approval status of the product such that an EUA is no longer needed.

For additional information about Emergency Use Authorization visit FDA at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization.

The Countermeasures Injury Compensation Program

The Countermeasures Injury Compensation Program (CICP) is a federal program that has been created to help pay for related costs of medical care and other specific expenses to compensate people injured after use of certain medical countermeasures. Medical countermeasures are specific vaccines, medications, devices, or other items used to prevent, diagnose, or treat the public during a public health emergency or a security threat. For more information about CICP regarding the Pfizer-BioNTech COVID-19 Vaccine used to prevent COVID-19, visit www.hrsa.gov/cicp, email cicp@hrsa.gov, or call: 1-855-266-2427.

Manufactured by
Pfizer Inc., New York, NY 10017

BIONTECH
Manufactured for
BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

LAB-1450-4.0

Revised: January 2021

END SHORT VERSION FACT SHEET
Long Version (Full EUA Prescribing Information) Begins On Next Page

FULL EMERGENCY USE AUTHORIZATION (EUA) PRESCRIBING INFORMATION

PFIZER-BIONTECH COVID-19 VACCINE

FULL EMERGENCY USE AUTHORIZATION PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full emergency use authorization prescribing information are not listed.

FULL EMERGENCY USE AUTHORIZATION (EUA) PRESCRIBING INFORMATION

1 AUTHORIZED USE

Pfizer-BioNTech COVID-19 Vaccine is authorized for use under an Emergency Use Authorization (EUA) for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older.

2 DOSAGE AND ADMINISTRATION

For intramuscular injection only.

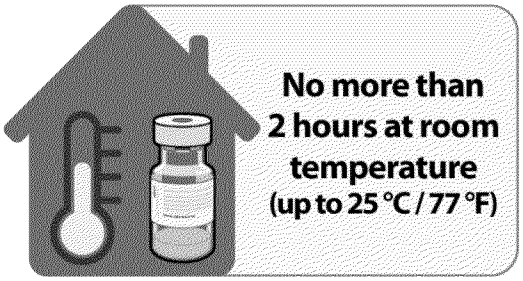
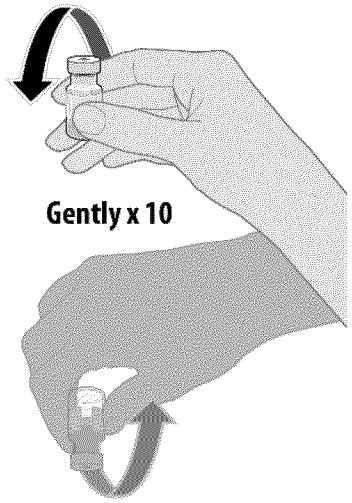
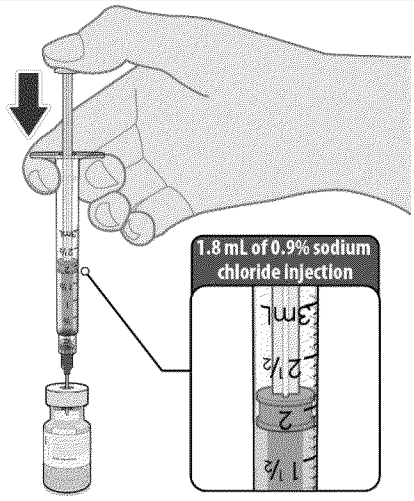
2.1 Preparation for Administration

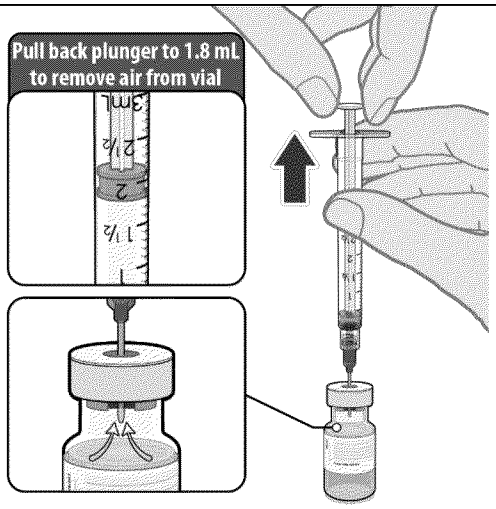
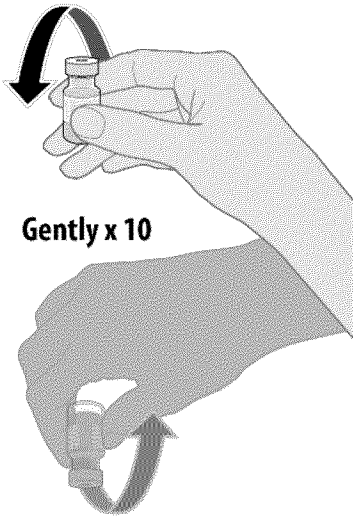
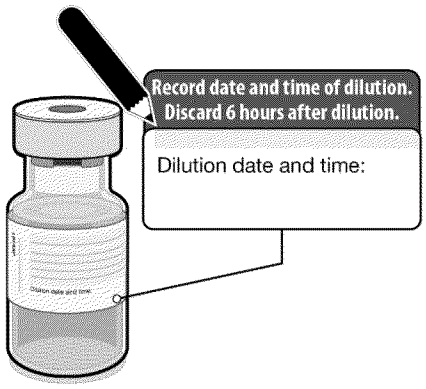
Prior to Dilution

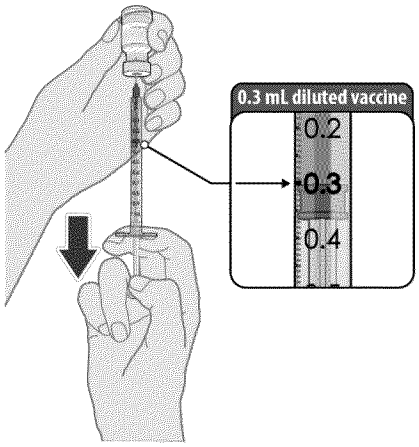
- The Pfizer-BioNTech COVID-19 Vaccine Multiple Dose Vial contains a volume of 0.45 mL, supplied as a frozen suspension that does not contain preservative. Each vial must be thawed and diluted prior to administration.
- Vials may be thawed in the refrigerator [2°C to 8°C (35°F to 46°F)] or at room temperature [up to 25°C (77°F)] *[see How Supplied/Storage and Handling (19)]*.
- Refer to thawing instructions in the panels below.

Dilution

- Dilute the vial contents using 1.8 mL of 0.9% Sodium Chloride Injection, USP (not provided) to form the Pfizer-BioNTech COVID-19 Vaccine. Do not add more than 1.8 mL of diluent.
- ONLY use 0.9% Sodium Chloride Injection, USP as the diluent. This diluent is not packaged with the vaccine and must be sourced separately. Do not use bacteriostatic 0.9% Sodium Chloride Injection or any other diluent.
- After dilution, one vial contains 6 doses of 0.3 mL. Vial labels and cartons may state that after dilution, a vial contains 5 doses of 0.3 mL. The information in this Full EUA Prescribing Information regarding the number of doses per vial after dilution supersedes the number of doses stated on vial labels and cartons.
- Refer to dilution and dose preparation instructions in the panels below.

THAWING PRIOR TO DILUTION	
	• Thaw vial(s) of Pfizer-BioNTech COVID-19 Vaccine before use either by: o Allowing vial(s) to thaw in the refrigerator [2°C to 8°C (35°F to 46°F)]. A carton of vials may take up to 3 hours to thaw, and thawed vials can be stored in the refrigerator for up to five days (120 hours). o Allowing vial(s) to sit at room temperature [up to 25°C (77°F)] for 30 minutes. • Using either thawing method, vials must reach room temperature before dilution and must be diluted within 2 hours.
	• Before dilution invert vaccine vial gently 10 times. • Do not shake. • Inspect the liquid in the vial prior to dilution. The liquid is a white to off-white suspension and may contain white to off-white opaque amorphous particles. • Do not use if liquid is discolored or if other particles are observed.
DILUTION	
	• Obtain sterile 0.9% Sodium Chloride Injection, USP. Use only this as the diluent. • Using aseptic technique, withdraw 1.8 mL of diluent into a transfer syringe (21-gauge or narrower needle). • Cleanse the vaccine vial stopper with a single-use antiseptic swab. • Add 1.8 mL of 0.9% Sodium Chloride Injection, USP into the vaccine vial.

	• Equalize vial pressure before removing the needle from the vial by withdrawing 1.8 mL air into the empty diluent syringe.
	• Gently invert the vial containing the Pfizer-BioNTech COVID-19 Vaccine 10 times to mix. • Do not shake. • Inspect the vaccine in the vial. • The vaccine will be an off-white suspension. Do not use if vaccine is discolored or contains particulate matter.
	• Record the date and time of dilution on the Pfizer-BioNTech COVID-19 Vaccine vial label. • Store between 2°C to 25°C (35°F to 77°F). • Discard any unused vaccine 6 hours after dilution.

PREPARATION OF INDIVIDUAL 0.3 mL DOSES OF PFIZER-BIONTECH COVID-19 VACCINE	
	• Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab, and withdraw 0.3 mL of the Pfizer-BioNTech COVID-19 Vaccine preferentially using low dead-volume syringes and/or needles. • 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. • Administer immediately.

2.2 Administration Information

Visually inspect each dose in the dosing syringe prior to administration. The vaccine will be an off-white suspension. During the visual inspection,

- verify the final dosing volume of 0.3 mL.
- confirm there are no particulates and that no discoloration is observed.
- do not administer if vaccine is discolored or contains particulate matter.

Administer the Pfizer-BioNTech COVID-19 Vaccine intramuscularly.

After dilution, vials of Pfizer-BioNTech COVID-19 Vaccine contain six doses of 0.3 mL of vaccine. Low dead-volume syringes and/or needles can be used to extract six 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.

2.3 Vaccination Schedule for Individuals 16 Years of Age and Older

The Pfizer-BioNTech COVID-19 Vaccine is administered intramuscularly as a series of two doses (0.3 mL each) three weeks apart.

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

3 DOSAGE FORMS AND STRENGTHS

Pfizer-BioNTech COVID-19 Vaccine is a suspension for injection. After preparation, a single dose is 0.3 mL.

4 CONTRAINDICATIONS

Do not administer Pfizer-BioNTech COVID-19 Vaccine to individuals with known history of a severe allergic reaction (e.g., anaphylaxis) to any component of the Pfizer-BioNTech COVID-19 Vaccine *[see Description (13)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Management of Acute Allergic Reactions

Appropriate medical treatment used to manage immediate allergic reactions must be immediately available in the event an acute anaphylactic reaction occurs following administration of Pfizer-BioNTech COVID-19 Vaccine.

Monitor Pfizer-BioNTech COVID-19 Vaccine recipients for the occurrence of immediate adverse reactions according to the Centers for Disease Control and Prevention guidelines (https://www.cdc.gov/vaccines/covid-19/).

5.2 Altered Immunocompetence

Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to the Pfizer-BioNTech COVID-19 Vaccine.

5.3 Limitation of Effectiveness

The Pfizer-BioNTech COVID-19 Vaccine may not protect all vaccine recipients.

6 OVERALL SAFETY SUMMARY

It is MANDATORY for vaccination providers to report to the Vaccine Adverse Event Reporting System (VAERS) all vaccine administration errors, all serious adverse events, cases of Multisystem Inflammatory Syndrome (MIS) in adults and children, and hospitalized or fatal cases of COVID-19 following vaccination with the Pfizer-BioNTech COVID-19 Vaccine. To the extent feasible, provide a copy of the VAERS form to Pfizer Inc. Please see the REQUIREMENTS AND INSTRUCTIONS FOR REPORTING ADVERSE EVENTS AND VACCINE ADMINISTRATION ERRORS section for details on reporting to VAERS and Pfizer Inc.

In clinical studies, adverse reactions in participants 16 years of age and older included pain at the injection site (84.1%), fatigue (62.9%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%), fever (14.2%), injection site swelling (10.5%), injection site redness (9.5%), nausea (1.1%), malaise (0.5%), and lymphadenopathy (0.3%).

Severe allergic reactions have been reported following the Pfizer-BioNTech COVID-19 Vaccine during mass vaccination outside of clinical trials.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of Pfizer-BioNTech COVID-19 Vaccine was evaluated in participants 16 years of age and older in two clinical studies conducted in the United States, Europe, Turkey, South Africa, and South America. Study BNT162-01 (Study 1) was a Phase 1/2, two-part, dose-escalation trial that enrolled 60 participants, 18 through 55 years of age. Study C4591001 (Study 2) is a Phase 1/2/3, multicenter, multinational, randomized, saline placebo-controlled, observer-blind, dose-finding, vaccine candidate-selection (Phase 1) and efficacy (Phase 2/3) study that has enrolled approximately 44,000 participants, 12 years of age or older. Of these, approximately 43,448 participants (21,720 Pfizer-BioNTech COVID-19 Vaccine; 21,728 placebo) in Phase 2/3 are 16 years of age or older (including 138 and 145 adolescents 16 and 17 years of age in the vaccine and placebo groups, respectively).

At the time of the analysis of Study 2 for the EUA, 37,586 (18,801 Pfizer-BioNTech COVID-19 Vaccine and 18,785 placebo) participants 16 years of age or older have been followed for a median of 2 months after the second dose of Pfizer-BioNTech COVID-19 Vaccine.

The safety evaluation in Study 2 is ongoing. The safety population includes participants enrolled by October 9, 2020, and includes safety data accrued through November 14, 2020. Participants 18 years and older in the reactogenicity subset are monitored for solicited local and systemic reactions and use of antipyretic medication after each vaccination in an electronic diary. Participants are being monitored for unsolicited adverse events, including serious adverse events, throughout the study [from Dose 1 through 1 month (all unsolicited adverse events) or 6 months (serious adverse events) after the last vaccination].

Demographic characteristics in Study 2 were generally similar with regard to age, gender, race, and ethnicity among participants who received Pfizer-BioNTech COVID-19 Vaccine and those who received placebo. Overall, among the total participants who received either the Pfizer-BioNTech COVID-19 Vaccine or placebo, 50.6% were male and 49.4% were female, 83.1% were White, 9.1% were Black or African American, 28.0% were Hispanic/Latino, 4.3% were Asian, and 0.5% were American Indian/Alaska Native.

Local and Systemic Adverse Reactions Solicited in the Study 2

Table 1 and Table 2 present the frequency and severity of solicited local and systemic reactions, respectively, within 7 days following each dose of Pfizer-BioNTech COVID-19 Vaccine and placebo in the subset of participants 18 to 55 years of age included in the EUA safety population who were monitored for reactogenicity with an electronic diary.

Table 3 and Table 4 present the frequency and severity of reported solicited local and systemic reactions, respectively, within 7 days of each dose of Pfizer-BioNTech COVID-19 Vaccine and placebo for participants 56 years of age and older.

Across both age groups, the mean duration of pain at the injection site after Dose 2 was 2.5 days (range 1 to 36 days), for redness 2.6 days (range 1 to 34 days), and for swelling 2.3 days (range 1 to 34 days) for participants in the Pfizer-BioNTech COVID-19 Vaccine group.

Solicited reactogenicity data in 16 and 17 year-old participants are limited.

Table 1: Study 2 – Frequency and Percentages of Participants with Solicited Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Participants 18-55 Years of Age‡ – Reactogenicity Subset of the Safety Population*

	Pfizer-BioNTech COVID-19 Vaccine Dose 1 N[a]=2291 n[b] (%)	Placebo Dose 1 N[a]=2298 n[b] (%)	Pfizer-BioNTech COVID-19 Vaccine Dose 2 N[a]=2098 n[b] (%)	Placebo Dose 2 N[a]=2103 n[b] (%)
Redness[c]				
Any (>2 cm)	104 (4.5)	26 (1.1)	123 (5.9)	14 (0.7)
Mild	70 (3.1)	16 (0.7)	73 (3.5)	8 (0.4)
Moderate	28 (1.2)	6 (0.3)	40 (1.9)	6 (0.3)
Severe	6 (0.3)	4 (0.2)	10 (0.5)	0 (0.0)
Swelling[c]				
Any (>2 cm)	132 (5.8)	11 (0.5)	132 (6.3)	5 (0.2)
Mild	88 (3.8)	3 (0.1)	80 (3.8)	3 (0.1)
Moderate	39 (1.7)	5 (0.2)	45 (2.1)	2 (0.1)
Severe	5 (0.2)	3 (0.1)	7 (0.3)	0 (0.0)
Pain at the injection site[d]				
Any	1904 (83.1)	322 (14.0)	1632 (77.8)	245 (11.7)
Mild	1170 (51.1)	308 (13.4)	1039 (49.5)	225 (10.7)
Moderate	710 (31.0)	12 (0.5)	568 (27.1)	20 (1.0)
Severe	24 (1.0)	2 (0.1)	25 (1.2)	0 (0.0)

Note: Reactions were collected in the electronic diary (e-diary) from Day 1 to Day 7 after vaccination.
a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.
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.
‡ Eight participants were between 16 and 17 years of age.
* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.

Table 2: Study 2 – Frequency and Percentages of Participants with Solicited Systemic Reactions, by Maximum Severity, Within 7 Days After Each Dose – Participants 18-55 Years of Age‡ – Safety Population*

	Pfizer-BioNTech COVID-19 Vaccine Dose 1 N[a]=2291 n[b] (%)	Placebo Dose 1 N[a]=2298 n[b] (%)	Pfizer-BioNTech COVID-19 Vaccine Dose 2 N[a]=2098 n[b] (%)	Placebo Dose 2 N[a]=2103 n[b] (%)
Fever				
≥38.0°C	85 (3.7)	20 (0.9)	331 (15.8)	10 (0.5)
≥38.0°C to 38.4°C	64 (2.8)	10 (0.4)	194 (9.2)	5 (0.2)
>38.4°C to 38.9°C	15 (0.7)	5 (0.2)	110 (5.2)	3 (0.1)
>38.9°C to 40.0°C	6 (0.3)	3 (0.1)	26 (1.2)	2 (0.1)
>40.0°C	0 (0.0)	2 (0.1)	1 (0.0)	0 (0.0)
Fatigue[c]				
Any	1085 (47.4)	767 (33.4)	1247 (59.4)	479 (22.8)
Mild	597 (26.1)	467 (20.3)	442 (21.1)	248 (11.8)
Moderate	455 (19.9)	289 (12.6)	708 (33.7)	217 (10.3)
Severe	33 (1.4)	11 (0.5)	97 (4.6)	14 (0.7)
Headache[c]				

	Pfizer-BioNTech COVID-19 Vaccine Dose 1 N[a]=2291 n[b] (%)	Placebo Dose 1 N[a]=2298 n[b] (%)	Pfizer-BioNTech COVID-19 Vaccine Dose 2 N[a]=2098 n[b] (%)	Placebo Dose 2 N[a]=2103 n[b] (%)
Any	959 (41.9)	775 (33.7)	1085 (51.7)	506 (24.1)
Mild	628 (27.4)	505 (22.0)	538 (25.6)	321 (15.3)
Moderate	308 (13.4)	251 (10.9)	480 (22.9)	170 (8.1)
Severe	23 (1.0)	19 (0.8)	67 (3.2)	15 (0.7)
Chills[c]				
Any	321 (14.0)	146 (6.4)	737 (35.1)	79 (3.8)
Mild	230 (10.0)	111 (4.8)	359 (17.1)	65 (3.1)
Moderate	82 (3.6)	33 (1.4)	333 (15.9)	14 (0.7)
Severe	9 (0.4)	2 (0.1)	45 (2.1)	0 (0.0)
Vomiting[d]				
Any	28 (1.2)	28 (1.2)	40 (1.9)	25 (1.2)
Mild	24 (1.0)	22 (1.0)	28 (1.3)	16 (0.8)
Moderate	4 (0.2)	5 (0.2)	8 (0.4)	9 (0.4)
Severe	0 (0.0)	1 (0.0)	4 (0.2)	0 (0.0)
Diarrhea[e]				
Any	255 (11.1)	270 (11.7)	219 (10.4)	177 (8.4)
Mild	206 (9.0)	217 (9.4)	179 (8.5)	144 (6.8)
Moderate	46 (2.0)	52 (2.3)	36 (1.7)	32 (1.5)
Severe	3 (0.1)	1 (0.0)	4 (0.2)	1 (0.0)
New or worsened muscle pain[c]				
Any	487 (21.3)	249 (10.8)	783 (37.3)	173 (8.2)
Mild	256 (11.2)	175 (7.6)	326 (15.5)	111 (5.3)
Moderate	218 (9.5)	72 (3.1)	410 (19.5)	59 (2.8)
Severe	13 (0.6)	2 (0.1)	47 (2.2)	3 (0.1)
New or worsened joint pain[c]				
Any	251 (11.0)	138 (6.0)	459 (21.9)	109 (5.2)
Mild	147 (6.4)	95 (4.1)	205 (9.8)	54 (2.6)
Moderate	99 (4.3)	43 (1.9)	234 (11.2)	51 (2.4)
Severe	5 (0.2)	0 (0.0)	20 (1.0)	4 (0.2)
Use of antipyretic or pain medication[f]	638 (27.8)	332 (14.4)	945 (45.0)	266 (12.6)

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

a. N = Number of participants reporting at least 1 yes or no response for the specified event after the specified dose.
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.
‡ Eight participants were between 16 and 17 years of age.
* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.

Table 3: Study 2 – Frequency and Percentages of Participants with Solicited Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Participants 56 Years of Age and Older – Safety Population*

	Pfizer-BioNTech COVID-19 Vaccine Dose 1 N[a]=1802 n[b] (%)	Placebo Dose 1 N[a]=1792 n[b] (%)	Pfizer-BioNTech COVID-19 Vaccine Dose 2 N[a]=1660 n[b] (%)	Placebo Dose 2 N[a]=1646 n[b] (%)
Redness[c]				
Any (>2 cm)	85 (4.7)	19 (1.1)	120 (7.2)	12 (0.7)
Mild	55 (3.1)	12 (0.7)	59 (3.6)	8 (0.5)
Moderate	27 (1.5)	5 (0.3)	53 (3.2)	3 (0.2)
Severe	3 (0.2)	2 (0.1)	8 (0.5)	1 (0.1)
Swelling[c]				
Any (>2 cm)	118 (6.5)	21 (1.2)	124 (7.5)	11 (0.7)
Mild	71 (3.9)	10 (0.6)	68 (4.1)	5 (0.3)
Moderate	45 (2.5)	11 (0.6)	53 (3.2)	5 (0.3)
Severe	2 (0.1)	0 (0.0)	3 (0.2)	1 (0.1)
Pain at the injection site[d]				
Any (>2 cm)	1282 (71.1)	166 (9.3)	1098 (66.1)	127 (7.7)
Mild	1008 (55.9)	160 (8.9)	792 (47.7)	125 (7.6)
Moderate	270 (15.0)	6 (0.3)	298 (18.0)	2 (0.1)
Severe	4 (0.2)	0 (0.0)	8 (0.5)	0 (0.0)

Note: Reactions were collected in the electronic diary (e-diary) from Day 1 to Day 7 after vaccination.
a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.
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.
* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.

Table 4: Study 2 – Frequency and Percentages of Participants with Solicited Systemic Reactions, by Maximum Severity, Within 7 Days After Each Dose – Participants 56 Years of Age and Older – Reactogenicity Subset of the Safety Population*

	Pfizer-BioNTech COVID-19 Vaccine Dose 1 N[a]=1802 n[b] (%)	Placebo Dose 1 N[a]=1792 n[b] (%)	Pfizer-BioNTech COVID-19 Vaccine Dose 2 N[a]=1660 n[b] (%)	Placebo Dose 2 N[a]=1646 n[b] (%)
Fever				
≥38.0°C	26 (1.4)	7 (0.4)	181 (10.9)	4 (0.2)
≥38.0°C to 38.4°C	23 (1.3)	2 (0.1)	131 (7.9)	2 (0.1)
>38.4°C to 38.9°C	1 (0.1)	3 (0.2)	45 (2.7)	1 (0.1)
>38.9°C to 40.0°C	1 (0.1)	2 (0.1)	5 (0.3)	1 (0.1)
>40.0°C	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue[c]				
Any	615 (34.1)	405 (22.6)	839 (50.5)	277 (16.8)
Mild	373 (20.7)	252 (14.1)	351 (21.1)	161 (9.8)
Moderate	240 (13.3)	150 (8.4)	442 (26.6)	114 (6.9)
Severe	2 (0.1)	3 (0.2)	46 (2.8)	2 (0.1)

	Pfizer-BioNTech COVID-19 Vaccine Dose 1 N[a]=1802 n[b] (%)	Placebo Dose 1 N[a]=1792 n[b] (%)	Pfizer-BioNTech COVID-19 Vaccine Dose 2 N[a]=1660 n[b] (%)	Placebo Dose 2 N[a]=1646 n[b] (%)
Headache[c]				
Any	454 (25.2)	325 (18.1)	647 (39.0)	229 (13.9)
Mild	348 (19.3)	242 (13.5)	422 (25.4)	165 (10.0)
Moderate	104 (5.8)	80 (4.5)	216 (13.0)	60 (3.6)
Severe	2 (0.1)	3 (0.2)	9 (0.5)	4 (0.2)
Chills[c]				
Any	113 (6.3)	57 (3.2)	377 (22.7)	46 (2.8)
Mild	87 (4.8)	40 (2.2)	199 (12.0)	35 (2.1)
Moderate	26 (1.4)	16 (0.9)	161 (9.7)	11 (0.7)
Severe	0 (0.0)	1 (0.1)	17 (1.0)	0 (0.0)
Vomiting[d]				
Any	9 (0.5)	9 (0.5)	11 (0.7)	5 (0.3)
Mild	8 (0.4)	9 (0.5)	9 (0.5)	5 (0.3)
Moderate	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)
Severe	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Diarrhea[e]				
Any	147 (8.2)	118 (6.6)	137 (8.3)	99 (6.0)
Mild	118 (6.5)	100 (5.6)	114 (6.9)	73 (4.4)
Moderate	26 (1.4)	17 (0.9)	21 (1.3)	22 (1.3)
Severe	3 (0.2)	1 (0.1)	2 (0.1)	4 (0.2)
New or worsened muscle pain[c]				
Any	251 (13.9)	149 (8.3)	477 (28.7)	87 (5.3)
Mild	168 (9.3)	100 (5.6)	202 (12.2)	57 (3.5)
Moderate	82 (4.6)	46 (2.6)	259 (15.6)	29 (1.8)
Severe	1 (0.1)	3 (0.2)	16 (1.0)	1 (0.1)
New or worsened joint pain[c]				
Any	155 (8.6)	109 (6.1)	313 (18.9)	61 (3.7)
Mild	101 (5.6)	68 (3.8)	161 (9.7)	35 (2.1)
Moderate	52 (2.9)	40 (2.2)	145 (8.7)	25 (1.5)
Severe	2 (0.1)	1 (0.1)	7 (0.4)	1 (0.1)
Use of antipyretic or pain medication	358 (19.9)	213 (11.9)	625 (37.7)	161 (9.8)

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

a. N = Number of participants reporting at least 1 yes or no response for the specified event after the specified dose.
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.
* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.

Unsolicited Adverse Events

Serious Adverse Events

In Study 2, among participants 16 to 55 years of age who had received at least 1 dose of vaccine or placebo (Pfizer-BioNTech COVID-19 Vaccine = 10,841; placebo = 10,851), serious adverse events from Dose 1 through up to 30 days after Dose 2 in ongoing follow-up were reported by 0.4% of Pfizer-BioNTech COVID-19 Vaccine recipients and by 0.3% of placebo recipients. In a similar analysis, in participants 56 years of age and older (Pfizer-BioNTech COVID-19 Vaccine = 7960, placebo = 7934), serious adverse events were reported by 0.8% of Pfizer-BioNTech COVID-19 Vaccine recipients and by 0.6% of placebo recipients who received at least 1 dose of Pfizer-BioNTech COVID-19 Vaccine or placebo, respectively. In these analyses, 91.6% of study participants had at least 30 days of follow-up after Dose 2. Appendicitis was reported as a serious adverse event for 12 participants, and numerically higher in the vaccine group, 8 vaccine participants and 4 placebo participants. Currently available information is insufficient to determine a causal relationship with the vaccine. There were no other notable patterns or numerical imbalances between treatment groups for specific categories of serious adverse events (including neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to Pfizer-BioNTech COVID-19 Vaccine.

Non-Serious Adverse Events

Overall in Study 2 in which 10,841 participants 16 to 55 years of age received Pfizer-BioNTech COVID-19 Vaccine and 10,851 participants received placebo, non-serious adverse events from Dose 1 through up to 30 days after Dose 2 in ongoing follow-up were reported in 29.3% of participants who received Pfizer-BioNTech COVID-19 Vaccine and 13.2% of participants in the placebo group, for participants who received at least 1 dose. Overall in a similar analysis in which 7960 participants 56 years of age and older received Pfizer-BioNTech COVID-19 Vaccine, non-serious adverse events within 30 days were reported in 23.8% of participants who received Pfizer-BioNTech COVID-19 Vaccine and 11.7% of participants in the placebo group, for participants who received at least 1 dose. In these analyses, 91.6% of study participants had at least 30 days of follow-up after Dose 2. The higher frequency of reported unsolicited non-serious adverse events among Pfizer BioNTech COVID-19 Vaccine recipients compared to placebo recipients was primarily attributed to local and systemic adverse events reported during the first 7 days following vaccination that are consistent with adverse reactions solicited among participants in the reactogenicity subset and presented in Tables 3 and 4. From Dose 1 through 30 days after Dose 2, reports of lymphadenopathy were imbalanced with notably more cases in the Pfizer-BioNTech COVID-19 Vaccine group (64) vs. the placebo group (6), which is plausibly related to vaccination. Throughout the safety follow-up period to date, Bell's palsy (facial paralysis) was reported by four participants in the Pfizer-BioNTech COVID-19 Vaccine group. Onset of facial paralysis was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of Bell's palsy were reported in the placebo group. Currently available information is insufficient to determine a causal relationship with the vaccine. There were no other notable patterns or numerical imbalances between treatment groups for specific categories of non-serious adverse events (including other neurologic or neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to Pfizer-BioNTech COVID-19 Vaccine.

8 REQUIREMENTS AND INSTRUCTIONS FOR REPORTING ADVERSE EVENTS AND VACCINE ADMINISTRATION ERRORS

See Overall Safety Summary (Section 6) for additional information.

The vaccination provider enrolled in the federal COVID-19 Vaccination Program is responsible for MANDATORY reporting of the listed events following Pfizer-BioNTech COVID-19 Vaccine to the Vaccine Adverse Event Reporting System (VAERS):

- Vaccine administration errors whether or not associated with an adverse event
- Serious adverse events* (irrespective of attribution to vaccination)
- Cases of Multisystem Inflammatory Syndrome (MIS) in children and adults
- Cases of COVID-19 that result in hospitalization or death

*Serious adverse events are defined as:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- An important medical event that based on appropriate medical judgement may jeopardize the individual and may require medical or surgical intervention to prevent one of the outcomes listed above

Instructions for Reporting to VAERS

The vaccination provider enrolled in the federal COVID-19 Vaccination Program should complete and submit a VAERS form to FDA using one of the following methods:

- Complete and submit the report online: https://vaers.hhs.gov/reportevent.html, or
- If you are unable to submit this form electronically, you may fax it to VAERS at 1-877-721-0366. If you need additional help submitting a report you may call the VAERS toll-free information line at 1-800-822-7967 or send an email to info@vaers.org.

IMPORTANT: When reporting adverse events or vaccine administration errors to VAERS, please complete the entire form with detailed information. It is important that the information reported to FDA be as detailed and complete as possible. Information to include:

- Patient demographics (e.g., patient name, date of birth)
- Pertinent medical history
- Pertinent details regarding admission and course of illness
- Concomitant medications
- Timing of adverse event(s) in relationship to administration of the Pfizer-BioNTech COVID-19 Vaccine
- Pertinent laboratory and virology information
- Outcome of the event and any additional follow-up information if it is available at the time of the VAERS report. Subsequent reporting of follow-up information should be completed if additional details become available.

The following steps are highlighted to provide the necessary information for safety tracking:

1. In Box 17, provide information on Pfizer-BioNTech COVID-19 Vaccine and any other vaccines administered on the same day; and in Box 22, provide information on any other vaccines received within one month prior.
2. In Box 18, description of the event:
    a. Write "Pfizer-BioNTech COVID-19 Vaccine EUA" as the first line.
    b. Provide a detailed report of vaccine administration error and/or adverse event. It is important to provide detailed information regarding the patient and adverse event/medication error for ongoing safety evaluation of this unapproved vaccine. Please see information to include listed above.

3. Contact information:
    a. In Box 13, provide the name and contact information of the prescribing healthcare provider or institutional designee who is responsible for the report.
    b. In Box 14, provide the name and contact information of the best doctor/healthcare professional to contact about the adverse event.
    c. In Box 15, provide the address of the facility where vaccine was given (NOT the healthcare provider's office address).

Other Reporting Instructions

Vaccination providers may report to VAERS other adverse events that are not required to be reported using the contact information above.

To the extent feasible, report adverse events to Pfizer Inc. using the contact information below or by providing a copy of the VAERS form to Pfizer Inc.

Website	Fax number	Telephone number
www.pfizersafetyreporting.com	1-866-635-8337	1-800-438-1985

10 DRUG INTERACTIONS

There are no data to assess the concomitant administration of the Pfizer-BioNTech COVID-19 Vaccine with other vaccines.

11 USE IN SPECIFIC POPULATIONS

11.1 Pregnancy

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Available data on Pfizer-BioNTech COVID-19 Vaccine administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

11.2 Lactation

Risk Summary

Data are not available to assess the effects of Pfizer-BioNTech COVID-19 Vaccine on the breastfed infant or on milk production/excretion.

11.3 Pediatric Use

Emergency Use Authorization of Pfizer-BioNTech COVID-19 Vaccine in adolescents 16 and 17 years of age is based on extrapolation of safety and effectiveness from adults 18 years of age and older. Emergency Use Authorization of Pfizer BioNTech COVID-19 Vaccine does not include use in individuals younger than 16 years of age.

11.4 Geriatric Use

Clinical studies of Pfizer-BioNTech COVID-19 Vaccine include participants 65 years of age and older and their data contributes to the overall assessment of safety and efficacy *[see Overall Safety Summary (6.1) and Clinical Trial Results and Supporting Data for EUA (18.1)]*. Of the total number of Pfizer-BioNTech COVID-19 Vaccine recipients in Study 2 (N=20,033), 21.4% (n=4,294) were 65 years of age and older and 4.3% (n=860) were 75 years of age and older.

13 DESCRIPTION

The Pfizer-BioNTech COVID-19 Vaccine is supplied as a frozen suspension in multiple dose vials; each vial must be diluted with 1.8 mL of sterile 0.9% Sodium Chloride Injection, USP prior to use to form the vaccine. Each dose of the Pfizer-BioNTech COVID-19 Vaccine contains 30 mcg of a nucleoside-modified messenger RNA (modRNA) encoding the viral spike (S) glycoprotein of SARS-CoV-2.

Each dose of the Pfizer-BioNTech COVID-19 Vaccine also includes the following ingredients: lipids (0.43 mg (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 0.05 mg 2[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 0.09 mg 1,2-distearoyl-sn-glycero-3-phosphocholine, and 0.2 mg cholesterol), 0.01 mg potassium chloride, 0.01 mg monobasic potassium phosphate, 0.36 mg sodium chloride, 0.07 mg dibasic sodium phosphate dihydrate, and 6 mg sucrose. The diluent (0.9% Sodium Chloride Injection, USP) contributes an additional 2.16 mg sodium chloride per dose.

The Pfizer-BioNTech COVID-19 Vaccine does not contain preservative. The vial stoppers are not made with natural rubber latex.

14 CLINICAL PHARMACOLOGY

14.1 Mechanism of Action

The modRNA in the Pfizer-BioNTech COVID-19 Vaccine is formulated in lipid particles, which enable delivery of the RNA into host cells to allow expression of the SARS-CoV-2 S antigen. The vaccine elicits an immune response to the S antigen, which protects against COVID-19.

18 CLINICAL TRIAL RESULTS AND SUPPORTING DATA FOR EUA

18.1 Efficacy in Participants 16 Years of Age and Older

Study 2 is a multicenter, multinational, Phase 1/2/3, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate–selection, and efficacy study in participants 12 years of age and older. Randomization was stratified by age: 12 through 15 years of age, 16 through 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥56-year stratum. The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19. Participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, were included as were participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV).

In the Phase 2/3 portion approximately 44,000 participants 12 years of age and older were randomized equally and received 2 doses of Pfizer-BioNTech COVID-19 Vaccine or placebo separated by 21 days. Participants are planned to be followed for up to 24 months, for assessments of safety and efficacy against COVID-19.

The population for the analysis of the primary efficacy endpoint included, 36,621 participants 12 years of age and older (18,242 in the Pfizer-BioNTech COVID-19 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. Table 5 presents the specific demographic characteristics in the studied population.

Table 5: Demographics (population for the primary efficacy endpoint)[a]

	Pfizer-BioNTech COVID-19 Vaccine (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 through 15 years	46 (0.3)	42 (0.2)
≥16 through 17 years	66 (0.4)	68 (0.4)
≥16 through 64 years	14,216 (77.9)	14,299 (77.8)
≥65 through 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 disease
   - 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)

Efficacy Against COVID-19

The population in the primary efficacy analysis included all participants 12 years of age and older who had been enrolled from July 27, 2020, and followed for the development of COVID-19 through November 14, 2020. Participants 18 to 55 years of age and 56 years of age and older began enrollment from July 27,2020, 16 to 17 years of age began enrollment from September 16, 2020 and 12 to 15 years of age began enrollment from October 15, 2020.

The 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

First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection*			
Subgroup	**Pfizer-BioNTech COVID-19 Vaccine 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 subjects[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 and older	1 0.508 (3848)	19 0.511 (3880)	94.7 (66.7, 99.9)[g]
First COVID-19 occurrence from 7 days after Dose 2 in participants with or without evidence of prior SARS-CoV-2 infection			
Subgroup	**Pfizer-BioNTech COVID-19 Vaccine 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 subjects[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 and older	1 0.530 (4044)	19 0.532 (4067)	94.7 (66.8, 99.9)[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).

* 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 participants 12 to 15 years of age.
f. Credible interval for 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. Confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.

19 HOW SUPPLIED/STORAGE AND HANDLING

Pfizer-BioNTech COVID-19 Vaccine Suspension for Intramuscular Injection, Multiple Dose Vials are supplied in a carton containing 25 multiple dose vials (NDC 59267-1000-3) or 195 multiple dose vials (NDC 59267-1000-2). After dilution, one vial contains 6 doses of 0.3 mL. Vial labels and cartons may state that after dilution, a vial contains 5 doses of 0.3 mL. The information in this Full EUA Prescribing Information regarding the number of doses per vial after dilution supersedes the number of doses stated on vial labels and cartons.

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

Do not refreeze thawed vials.

Frozen Vials Prior to Use

Cartons of Pfizer-BioNTech COVID-19 Vaccine Multiple Dose Vials arrive in thermal containers with dry ice. Once received, remove the vial cartons immediately from the thermal container and store in an ultra-low temperature freezer between -80°C to -60°C (-112°F to -76°F). Vials must be kept frozen between -80°C to -60°C (-112°F to -76°F) and protected from light, in the original cartons, until ready to use.

If an ultra-low temperature freezer is not available, the thermal container in which the Pfizer-BioNTech COVID-19 Vaccine arrives may be used as temporary storage when consistently re-filled to the top of the container with dry ice. Refer to the re-icing guidelines packed in the original thermal container for instructions regarding the use of the thermal container for temporary storage. The thermal container maintains a temperature range of -90°C to -60°C (-130°F to -76°F). Storage within this temperature range is not considered an excursion from the recommended storage condition.

Thawed Vials Before Dilution

Thawed Under Refrigeration
Thaw and then store undiluted vials in the refrigerator [2°C to 8°C (35°F to 46°F)] for up to 5 days (120 hours). A carton of 25 vials or 195 vials may take up to 2 or 3 hours, respectively, to thaw in the refrigerator, whereas a fewer number of vials will thaw in less time.

Thawed at Room Temperature
For immediate use, thaw undiluted vials at room temperature [up to 25°C (77°F)] for 30 minutes. Thawed vials can be handled in room light conditions.

Vials must reach room temperature before dilution.

Undiluted vials may be stored at room temperature for no more than 2 hours.

Vials After Dilution

After dilution, store vials between 2°C to 25°C (35°F to 77°F) and use within 6 hours from the time of dilution. During storage, minimize exposure to room light, and avoid exposure to direct sunlight and ultraviolet light. Any vaccine remaining in vials must be discarded after 6 hours. Do not refreeze.

20 PATIENT COUNSELING INFORMATION

Advise the recipient or caregiver to read the Fact Sheet for Recipients and Caregivers.

The vaccination provider must include vaccination information in the state/local jurisdiction's Immunization Information System (IIS) or other designated system. Advise recipient or caregiver that more information about IISs can be found at: https://www.cdc.gov/vaccines/programs/iis/about.html.

21 CONTACT INFORMATION

For general questions, visit the website or call the telephone number provided below.

Website	Telephone number
www.cvdvaccine.com	1-877-829-2619 (1-877-VAX-CO19)

This Full EUA Prescribing Information may have been updated. For the most recent Full EUA Prescribing Information, please see www.cvdvaccine.com.

Manufactured by
Pfizer Inc., New York, NY 10017

Manufactured for
BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

LAB-1457-4.0

Revised: January 2021

FACT SHEET FOR HEALTHCARE PROVIDERS ADMINISTERING VACCINE (VACCINATION PROVIDERS)

EMERGENCY USE AUTHORIZATION (EUA) OF THE PFIZER-BIONTECH COVID-19 VACCINE TO PREVENT CORONAVIRUS DISEASE 2019 (COVID-19)

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product, **Pfizer-BioNTech COVID-19 Vaccine**, for active immunization to prevent COVID-19 in individuals 16 years of age and older.

SUMMARY OF INSTRUCTIONS FOR COVID-19 VACCINATION PROVIDERS

Vaccination providers enrolled in the federal COVID-19 Vaccination Program must report all vaccine administration errors, all serious adverse events, cases of Multisystem Inflammatory Syndrome (MIS) in adults and children, and cases of COVID-19 that result in hospitalization or death following administration of Pfizer-BioNTech COVID-19 Vaccine. See "MANDATORY REQUIREMENTS FOR PFIZER-BIONTECH COVID-19 VACCINE ADMINISTRATION UNDER EMERGENCY USE AUTHORIZATION" for reporting requirements.

The Pfizer-BioNTech COVID-19 Vaccine is a suspension for intramuscular injection administered as a series of two doses (0.3 mL each) 3 weeks apart.

See this Fact Sheet for instructions for preparation and administration. This Fact Sheet may have been updated. For the most recent Fact Sheet, please see www.cvdvaccine.com.

For information on clinical trials that are testing the use of the Pfizer-BioNTech COVID-19 Vaccine for active immunization against COVID-19, please see www.clinicaltrials.gov.

DESCRIPTION OF COVID-19

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the novel coronavirus, SARS-CoV-2, that appeared in late 2019. It is predominantly a respiratory illness that can affect other organs. People with COVID-19 have reported a wide range of symptoms, ranging from mild symptoms to severe illness. Symptoms may appear 2 to 14 days after exposure to the virus. Symptoms may include: fever or chills; cough; shortness of breath; fatigue; muscle or body aches; headache; new loss of taste or smell; sore throat; congestion or runny nose; nausea or vomiting; diarrhea.

DOSAGE AND ADMINISTRATION

Storage and Handling

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

Do not refreeze thawed vials.

Frozen Vials Prior to Use

Cartons of Pfizer-BioNTech COVID-19 Vaccine Multiple Dose Vials arrive in thermal containers with dry ice. Once received, remove the vial cartons immediately from the thermal container and store in an ultra-low temperature freezer between -80ºC to -60ºC (-112ºF to -76ºF). Vials must be kept frozen between -80ºC to -60ºC (-112ºF to -76ºF) and protected from light until ready to use.

If an ultra-low temperature freezer is not available, the thermal container in which the Pfizer-BioNTech COVID-19 Vaccine arrives may be used as temporary storage when consistently re-filled to the top of the container with dry ice. Refer to the re-icing guidelines packed in the original thermal container for instructions regarding the use of the thermal container for temporary storage. The thermal container maintains a temperature range of -90ºC to -60ºC (-130ºF to -76ºF). Storage of the vials between -96°C to -60°C (-141°F to -76°F) is not considered an excursion from the recommended storage condition.

Thawed Vials Before Dilution

Thawed Under Refrigeration
Thaw and then store undiluted vials in the refrigerator [2ºC to 8ºC (35ºF to 46ºF)] for up to 5 days (120 hours). A carton of 25 vials or 195 vials may take up to 2 or 3 hours, respectively, to thaw in the refrigerator, whereas a fewer number of vials will thaw in less time.

Transportation at 2°C to 8°C (35°F to 46°F)
If local redistribution is needed and full cartons containing vials cannot be transported at -90°C to -60°C (-130°F to -76°F), available data support transportation of one or more thawed vials at 2°C to 8°C (35°F to 46°F) for up to 12 hours. Any hours used for transport at 2°C to 8°C (35°F to 46°F) count against the 120-hour limit for storage at 2°C to 8°C (35°F to 46°F).

Thawed at Room Temperature
For immediate use, thaw undiluted vials at room temperature [up to 25ºC (77ºF)] for 30 minutes. Thawed vials can be handled in room light conditions. Vials must reach room temperature before dilution.

Undiluted vials may be stored at room temperature for no more than 2 hours.

Vials After Dilution

- After dilution, store vials between 2°C to 25°C (35°F to 77°F) and use within 6 hours from the time of dilution.
- During storage, minimize exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.
- Any vaccine remaining in vials must be discarded after 6 hours.
- Do not refreeze.

Dosing and Schedule

The Pfizer-BioNTech COVID-19 Vaccine is administered intramuscularly as a series of two doses (0.3 mL each) 3 weeks apart.

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

Dose Preparation

Prior to Dilution

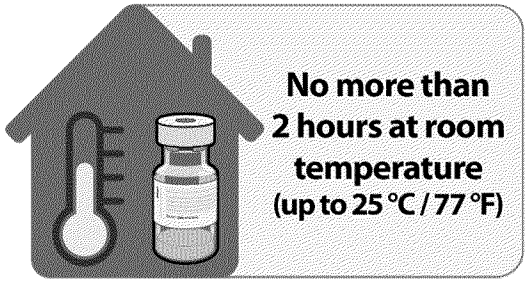
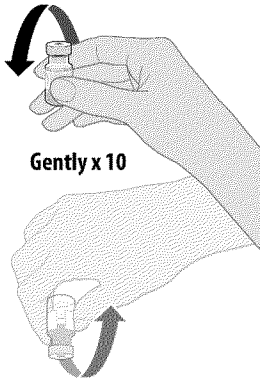
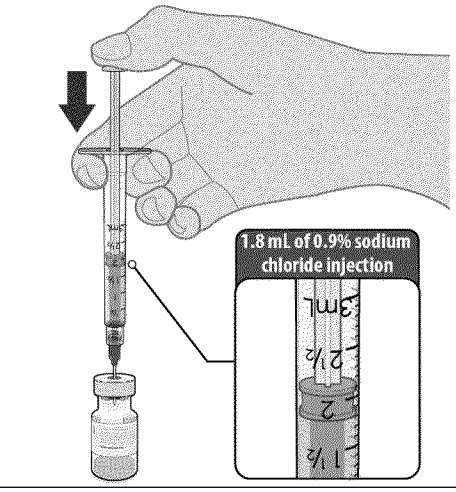
- The Pfizer-BioNTech COVID-19 Vaccine Multiple Dose Vial contains a volume of 0.45 mL, supplied as a frozen suspension that does not contain preservative. Each vial must be thawed and diluted prior to administration.
- Vials may be thawed in the refrigerator [2ºC to 8ºC (35ºF to 46ºF)] or at room temperature [up to 25ºC (77ºF)] *(see Storage and Handling)*.
- Refer to thawing instructions in the panels below.

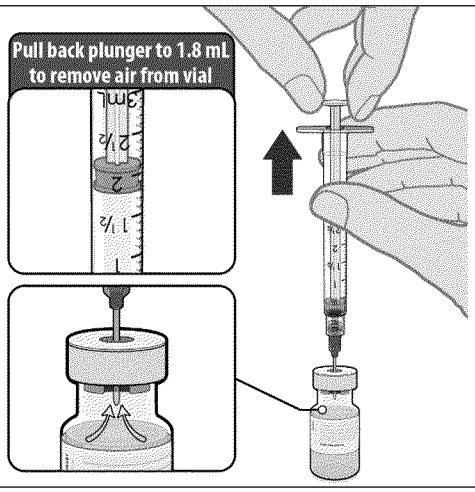
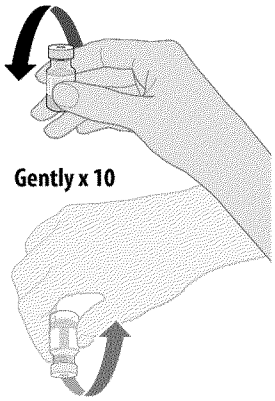
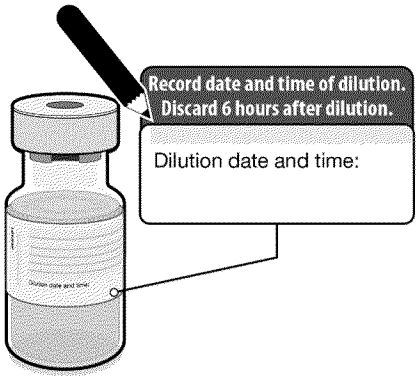
Dilution

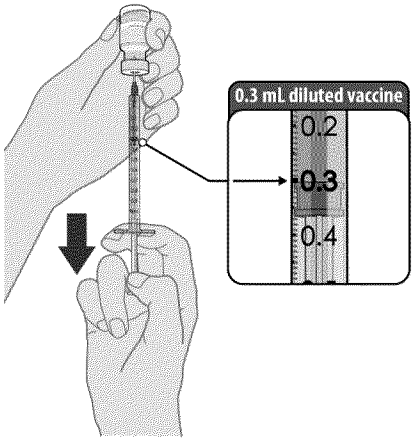
Dilute the vial contents using 1.8 mL of 0.9% Sodium Chloride Injection, USP (not provided) to form the Pfizer-BioNTech COVID-19 Vaccine. ONLY use 0.9% Sodium Chloride Injection, USP as the diluent. This diluent is not packaged with the vaccine and must be sourced separately. Do not use bacteriostatic 0.9% Sodium Chloride Injection or any other diluent. Do not add more than 1.8 mL of diluent.

After dilution, one vial contains 6 doses of 0.3 mL. Vial labels and cartons may state that after dilution, a vial contains 5 doses of 0.3 mL. The information in this Fact Sheet regarding the number of doses per vial after dilution supersedes the number of doses stated on vial labels and cartons.

- Refer to dilution and dose preparation instructions in the panels below.

THAWING PRIOR TO DILUTION	
	• Thaw vial(s) of Pfizer-BioNTech COVID-19 Vaccine before use either by: o Allowing vial(s) to thaw in the refrigerator [2ºC to 8ºC (35ºF to 46ºF)]. A carton of vials may take up to 3 hours to thaw, and thawed vials can be stored in the refrigerator for up to five days (120 hours). o Allowing vial(s) to sit at room temperature [up to 25ºC (77ºF)] for 30 minutes. • Using either thawing method, vials must reach room temperature before dilution and must be diluted within 2 hours.
	• Before dilution invert vaccine vial gently 10 times. • Do not shake. • Inspect the liquid in the vial prior to dilution. The liquid is a white to off-white suspension and may contain white to off-white opaque amorphous particles. • Do not use if liquid is discolored or if other particles are observed.
DILUTION	
	• Obtain sterile 0.9% Sodium Chloride Injection, USP. Use only this as the diluent. • Using aseptic technique, withdraw 1.8 mL of diluent into a transfer syringe (21-gauge or narrower needle). • Cleanse the vaccine vial stopper with a single-use antiseptic swab. • Add 1.8 mL of 0.9% Sodium Chloride Injection, USP into the vaccine vial.

	• Equalize vial pressure before removing the needle from the vial by withdrawing 1.8 mL air into the empty diluent syringe.
	• Gently invert the vial containing the Pfizer-BioNTech COVID-19 Vaccine 10 times to mix. • Do not shake. • Inspect the vaccine in the vial. • The vaccine will be an off-white suspension. Do not use if vaccine is discolored or contains particulate matter.
	• Record the date and time of dilution on the Pfizer-BioNTech COVID-19 Vaccine vial label. • Store between 2°C to 25°C (35°F to 77°F). • Discard any unused vaccine 6 hours after dilution.

PREPARATION OF INDIVIDUAL 0.3 mL DOSES OF PFIZER-BIONTECH COVID-19 VACCINE	
	• Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab, and withdraw 0.3 mL of the Pfizer-BioNTech COVID-19 Vaccine preferentially using a low dead-volume syringe and/or 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. • Administer immediately.

Administration

Visually inspect each dose in the dosing syringe prior to administration. The vaccine will be an off-white suspension. During the visual inspection,

- verify the final dosing volume of 0.3 mL.
- confirm there are no particulates and that no discoloration is observed.
- do not administer if vaccine is discolored or contains particulate matter.

Administer the Pfizer-BioNTech COVID-19 Vaccine intramuscularly.

After dilution, vials of Pfizer-BioNTech COVID-19 Vaccine contain six doses of 0.3mL of vaccine. Low dead-volume syringes and/or needles can be used to extract six 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 content.
- Do not pool excess vaccine from multiple vials.

Contraindications

Do not administer Pfizer-BioNTech COVID-19 Vaccine to individuals with known history of a severe allergic reaction (e.g., anaphylaxis) to any component of the Pfizer-BioNTech COVID-19 Vaccine *(see Full EUA Prescribing Information)*.

Warnings

Appropriate medical treatment used to manage immediate allergic reactions must be immediately available in the event an acute anaphylactic reaction occurs following administration of Pfizer-BioNTech COVID-19 Vaccine.

Monitor Pfizer-BioNTech COVID-19 Vaccine recipients for the occurrence of immediate adverse reactions according to the Centers for Disease Control and Prevention guidelines (https://www.cdc.gov/vaccines/covid-19/).

Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to the Pfizer-BioNTech COVID-19 Vaccine.

Pfizer-BioNTech COVID-19 Vaccine may not protect all vaccine recipients.

Adverse Reactions

Adverse reactions following the Pfizer-BioNTech COVID-19 Vaccine that have been reported in clinical trials include injection site pain, fatigue, headache, muscle pain, chills, joint pain, fever, injection site swelling, injection site redness, nausea, malaise, and lymphadenopathy *(see Full EUA Prescribing Information)*.

Severe allergic reactions, including anaphylaxis, have been reported following the Pfizer-BioNTech COVID-19 Vaccine during mass vaccination outside of clinical trials.

Additional adverse reactions, some of which may be serious, may become apparent with more widespread use of the Pfizer-BioNTech COVID-19 Vaccine.

Use with Other Vaccines

There is no information on the co-administration of the Pfizer-BioNTech COVID-19 Vaccine with other vaccines.

INFORMATION TO PROVIDE TO VACCINE RECIPIENTS/CAREGIVERS

As the vaccination provider, you must communicate to the recipient or their caregiver, information consistent with the "Fact Sheet for Recipients and Caregivers" (and provide a copy or direct the individual to the website www.cvdvaccine.com to obtain the Fact Sheet) prior to the individual receiving each dose of Pfizer-BioNTech COVID-19 Vaccine, including:

- FDA has authorized the emergency use of the Pfizer-BioNTech COVID-19 Vaccine, which is not an FDA-approved vaccine.
- The recipient or their caregiver has the option to accept or refuse Pfizer-BioNTech COVID-19 Vaccine.

- The significant known and potential risks and benefits of Pfizer-BioNTech COVID-19 Vaccine, and the extent to which such risks and benefits are unknown.
- Information about available alternative vaccines and the risks and benefits of those alternatives.

For information on clinical trials that are testing the use of the Pfizer-BioNTech COVID-19 Vaccine to prevent COVID-19, please see www.clinicaltrials.gov.

Provide a vaccination card to the recipient or their caregiver with the date when the recipient needs to return for the second dose of Pfizer-BioNTech COVID-19 Vaccine.

Provide the v-safe information sheet to vaccine recipients/caregivers and encourage vaccine recipients to participate in v-safe. V-safe is a new voluntary smartphone-based tool that uses text messaging and web surveys to check in with people who have been vaccinated to identify potential side effects after COVID-19 vaccination. V-safe asks questions that help CDC monitor the safety of COVID-19 vaccines. V-safe also provides second-dose reminders if needed and live telephone follow-up by CDC if participants report a significant health impact following COVID-19 vaccination. For more information, visit: www.cdc.gov/vsafe.

MANDATORY REQUIREMENTS FOR PFIZER-BIONTECH COVID-19 VACCINE ADMINISTRATION UNDER EMERGENCY USE AUTHORIZATION

In order to mitigate the risks of using this unapproved product under EUA and to optimize the potential benefit of Pfizer-BioNTech COVID-19 Vaccine, the following items are required. Use of unapproved Pfizer-BioNTech COVID-19 Vaccine for active immunization to prevent COVID-19 under this EUA is limited to the following (all requirements **must** be met):

1. Pfizer-BioNTech COVID-19 Vaccine is authorized for use in individuals 16 years of age and older.

2. The vaccination provider must communicate to the individual receiving the Pfizer-BioNTech COVID-19 Vaccine or their caregiver, information consistent with the "Fact Sheet for Recipients and Caregivers" prior to the individual receiving Pfizer-BioNTech COVID-19 Vaccine.

3. The vaccination provider must include vaccination information in the state/local jurisdiction's Immunization Information System (IIS) or other designated system.

4. The vaccination provider is responsible for mandatory reporting of the following to the Vaccine Adverse Event Reporting System (VAERS):
    - vaccine administration errors whether or not associated with an adverse event,
    - serious adverse events* (irrespective of attribution to vaccination),

- cases of Multisystem Inflammatory Syndrome (MIS) in adults and children, and
- cases of COVID-19 that result in hospitalization or death.

Complete and submit reports to VAERS online at https://vaers.hhs.gov/reportevent.html. For further assistance with reporting to VAERS call 1-800-822-7967. The reports should include the words "Pfizer-BioNTech COVID-19 Vaccine EUA" in the description section of the report.

5. The vaccination provider is responsible for responding to FDA requests for information about vaccine administration errors, adverse events, cases of MIS in adults and children, and cases of COVID-19 that result in hospitalization or death following administration of Pfizer-BioNTech COVID-19 Vaccine to recipients.

* Serious adverse events are defined as:
- Death;
- A life-threatening adverse event;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect;
- An important medical event that based on appropriate medical judgement may jeopardize the individual and may require medical or surgical intervention to prevent one of the outcomes listed above.

OTHER ADVERSE EVENT REPORTING TO VAERS AND PFIZER INC.

Vaccination providers may report to VAERS other adverse events that are not required to be reported using the contact information above.

To the extent feasible, report adverse events to Pfizer Inc. using the contact information below or by providing a copy of the VAERS form to Pfizer Inc.

Website	Fax number	Telephone number
www.pfizersafetyreporting.com	1-866-635-8337	1-800-438-1985

ADDITIONAL INFORMATION

For general questions, visit the website or call the telephone number provided below.

To access the most recent Pfizer-BioNTech COVID-19 Vaccine Fact Sheets, please scan the QR code provided below.

Global website	Telephone number
www.cvdvaccine.com	1-877-829-2619 (1-877-VAX-CO19)

AVAILABLE ALTERNATIVES

There is no approved alternative vaccine to prevent COVID-19. There may be clinical trials or availability under EUA of other COVID-19 vaccines.

AUTHORITY FOR ISSUANCE OF THE EUA

The Secretary of Health and Human Services (HHS) has declared a public health emergency that justifies the emergency use of drugs and biological products during the COVID-19 pandemic. In response, FDA has issued an EUA for the unapproved product, Pfizer-BioNTech COVID-19 Vaccine, for active immunization against COVID-19 in individuals 16 years of age and older.

FDA issued this EUA, based on Pfizer-BioNTech's request and submitted data.

Although limited scientific information is available, based on the totality of the scientific evidence available to date, it is reasonable to believe that the Pfizer-BioNTech COVID-19 Vaccine may be effective for the prevention of COVID-19 in individuals as specified in the *Full EUA Prescribing Information*.

This EUA for the Pfizer-BioNTech COVID-19 Vaccine will end when the Secretary of HHS determines that the circumstances justifying the EUA no longer exist or when there is a change in the approval status of the product such that an EUA is no longer needed.

For additional information about Emergency Use Authorization visit FDA at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization.

The Countermeasures Injury Compensation Program

The Countermeasures Injury Compensation Program (CICP) is a federal program that has been created to help pay for related costs of medical care and other specific expenses to compensate people injured after use of certain medical countermeasures. Medical countermeasures are specific vaccines, medications, devices, or other items used to prevent, diagnose, or treat the public during a public health emergency or a security threat. For more information about CICP regarding the Pfizer-BioNTech COVID-19 Vaccine used to prevent COVID-19, visit www.hrsa.gov/cicp, email cicp@hrsa.gov, or call: 1-855-266-2427.

Manufactured by
Pfizer Inc., New York, NY 10017

BIONTECH
Manufactured for
BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

LAB-1450-5.0

Revised: January 2021

END SHORT VERSION FACT SHEET
Long Version (Full EUA Prescribing Information) Begins On Next Page

FULL EMERGENCY USE AUTHORIZATION (EUA) PRESCRIBING INFORMATION

PFIZER-BIONTECH COVID-19 VACCINE

FULL EMERGENCY USE AUTHORIZATION PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full emergency use authorization prescribing information are not listed.

FULL EMERGENCY USE AUTHORIZATION (EUA) PRESCRIBING INFORMATION

1 AUTHORIZED USE

Pfizer-BioNTech COVID-19 Vaccine is authorized for use under an Emergency Use Authorization (EUA) for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older.

2 DOSAGE AND ADMINISTRATION

For intramuscular injection only.

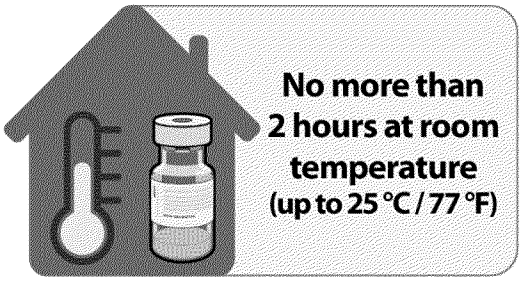
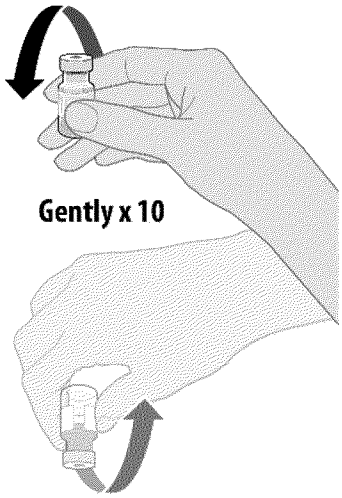
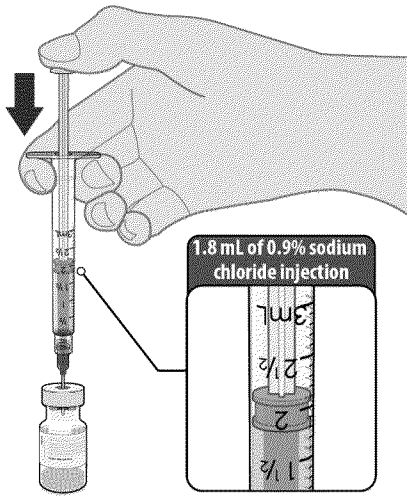
2.1 Preparation for Administration

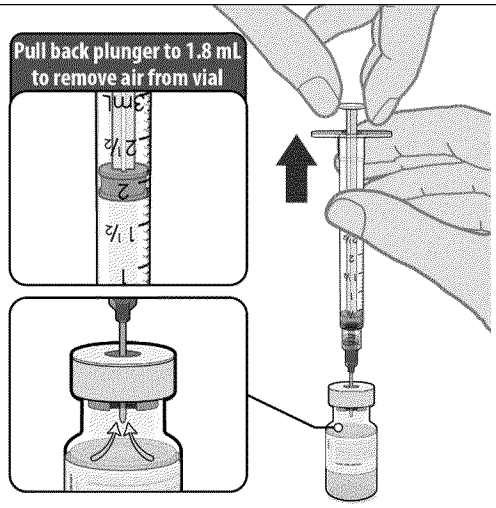
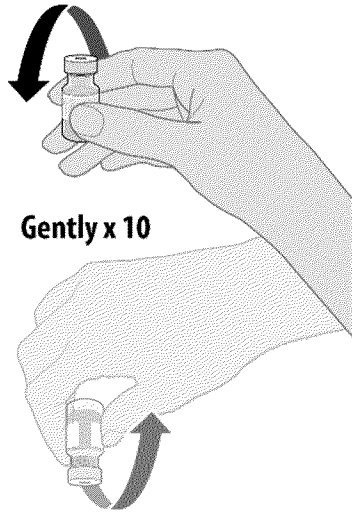
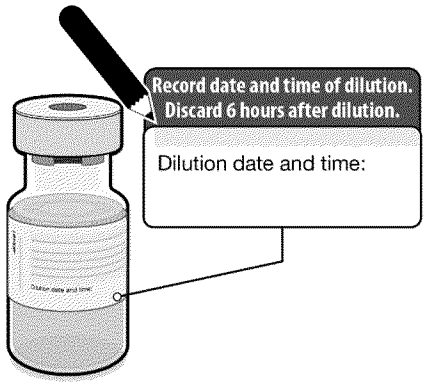
Prior to Dilution

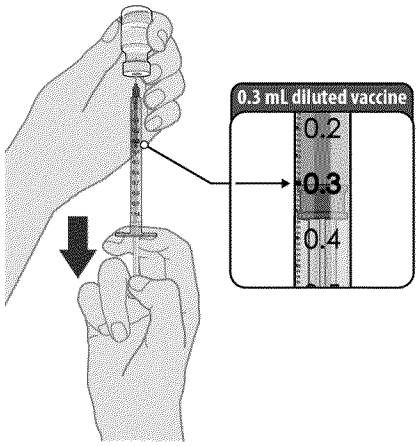
- The Pfizer-BioNTech COVID-19 Vaccine Multiple Dose Vial contains a volume of 0.45 mL, supplied as a frozen suspension that does not contain preservative. Each vial must be thawed and diluted prior to administration.
- Vials may be thawed in the refrigerator [2°C to 8°C (35°F to 46°F)] or at room temperature [up to 25°C (77°F)] *[see How Supplied/Storage and Handling (19)]*.
- Refer to thawing instructions in the panels below.

Dilution

- Dilute the vial contents using 1.8 mL of 0.9% Sodium Chloride Injection, USP (not provided) to form the Pfizer-BioNTech COVID-19 Vaccine. Do not add more than 1.8 mL of diluent.
- ONLY use 0.9% Sodium Chloride Injection, USP as the diluent. This diluent is not packaged with the vaccine and must be sourced separately. Do not use bacteriostatic 0.9% Sodium Chloride Injection or any other diluent.
- After dilution, one vial contains 6 doses of 0.3 mL. Vial labels and cartons may state that after dilution, a vial contains 5 doses of 0.3 mL. The information in this Full EUA Prescribing Information regarding the number of doses per vial after dilution supersedes the number of doses stated on vial labels and cartons.
- Refer to dilution and dose preparation instructions in the panels below.

THAWING PRIOR TO DILUTION	
	• Thaw vial(s) of Pfizer-BioNTech COVID-19 Vaccine before use either by: o Allowing vial(s) to thaw in the refrigerator [2ºC to 8ºC (35ºF to 46ºF)]. A carton of vials may take up to 3 hours to thaw, and thawed vials can be stored in the refrigerator for up to five days (120 hours). o Allowing vial(s) to sit at room temperature [up to 25ºC (77ºF)] for 30 minutes. • Using either thawing method, vials must reach room temperature before dilution and must be diluted within 2 hours.
	• Before dilution invert vaccine vial gently 10 times. • Do not shake. • Inspect the liquid in the vial prior to dilution. The liquid is a white to off-white suspension and may contain white to off-white opaque amorphous particles. • Do not use if liquid is discolored or if other particles are observed.
DILUTION	
	• Obtain sterile 0.9% Sodium Chloride Injection, USP. Use only this as the diluent. • Using aseptic technique, withdraw 1.8 mL of diluent into a transfer syringe (21-gauge or narrower needle). • Cleanse the vaccine vial stopper with a single-use antiseptic swab. • Add 1.8 mL of 0.9% Sodium Chloride Injection, USP into the vaccine vial.

	• Equalize vial pressure before removing the needle from the vial by withdrawing 1.8 mL air into the empty diluent syringe.
	• Gently invert the vial containing the Pfizer-BioNTech COVID-19 Vaccine 10 times to mix. • Do not shake. • Inspect the vaccine in the vial. • The vaccine will be an off-white suspension. Do not use if vaccine is discolored or contains particulate matter.
	• Record the date and time of dilution on the Pfizer-BioNTech COVID-19 Vaccine vial label. • Store between 2°C to 25°C (35°F to 77°F). • Discard any unused vaccine 6 hours after dilution.

PREPARATION OF INDIVIDUAL 0.3 mL DOSES OF PFIZER-BIONTECH COVID-19 VACCINE	
	• Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab, and withdraw 0.3 mL of the Pfizer-BioNTech COVID-19 Vaccine preferentially using low dead-volume syringes and/or needles. • 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. • Administer immediately.

2.2 Administration Information

Visually inspect each dose in the dosing syringe prior to administration. The vaccine will be an off-white suspension. During the visual inspection,

- verify the final dosing volume of 0.3 mL.
- confirm there are no particulates and that no discoloration is observed.
- do not administer if vaccine is discolored or contains particulate matter.

Administer the Pfizer-BioNTech COVID-19 Vaccine intramuscularly.

After dilution, vials of Pfizer-BioNTech COVID-19 Vaccine contain six doses of 0.3 mL of vaccine. Low dead-volume syringes and/or needles can be used to extract six 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.

2.3 Vaccination Schedule for Individuals 16 Years of Age and Older

The Pfizer-BioNTech COVID-19 Vaccine is administered intramuscularly as a series of two doses (0.3 mL each) three weeks apart.

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

3 DOSAGE FORMS AND STRENGTHS

Pfizer-BioNTech COVID-19 Vaccine is a suspension for injection. After preparation, a single dose is 0.3 mL.

4 CONTRAINDICATIONS

Do not administer Pfizer-BioNTech COVID-19 Vaccine to individuals with known history of a severe allergic reaction (e.g., anaphylaxis) to any component of the Pfizer-BioNTech COVID-19 Vaccine *[see Description (13)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Management of Acute Allergic Reactions

Appropriate medical treatment used to manage immediate allergic reactions must be immediately available in the event an acute anaphylactic reaction occurs following administration of Pfizer-BioNTech COVID-19 Vaccine.

Monitor Pfizer-BioNTech COVID-19 Vaccine recipients for the occurrence of immediate adverse reactions according to the Centers for Disease Control and Prevention guidelines (https://www.cdc.gov/vaccines/covid-19/).

5.2 Altered Immunocompetence

Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to the Pfizer-BioNTech COVID-19 Vaccine.

5.3 Limitation of Effectiveness

The Pfizer-BioNTech COVID-19 Vaccine may not protect all vaccine recipients.

6 OVERALL SAFETY SUMMARY

It is MANDATORY for vaccination providers to report to the Vaccine Adverse Event Reporting System (VAERS) all vaccine administration errors, all serious adverse events, cases of Multisystem Inflammatory Syndrome (MIS) in adults and children, and hospitalized or fatal cases of COVID-19 following vaccination with the Pfizer-BioNTech COVID-19 Vaccine. To the extent feasible, provide a copy of the VAERS form to Pfizer Inc. Please see the REQUIREMENTS AND INSTRUCTIONS FOR REPORTING ADVERSE EVENTS AND VACCINE ADMINISTRATION ERRORS section for details on reporting to VAERS and Pfizer Inc.

In clinical studies, adverse reactions in participants 16 years of age and older included pain at the injection site (84.1%), fatigue (62.9%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%), fever (14.2%), injection site swelling (10.5%), injection site redness (9.5%), nausea (1.1%), malaise (0.5%), and lymphadenopathy (0.3%).

Severe allergic reactions, including anaphylaxis, have been reported following the Pfizer-BioNTech COVID-19 Vaccine during mass vaccination outside of clinical trials.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of Pfizer-BioNTech COVID-19 Vaccine was evaluated in participants 16 years of age and older in two clinical studies conducted in the United States, Europe, Turkey, South Africa, and South America. Study BNT162-01 (Study 1) was a Phase 1/2, two-part, dose-escalation trial that enrolled 60 participants, 18 through 55 years of age. Study C4591001 (Study 2) is a Phase 1/2/3, multicenter, multinational, randomized, saline placebo-controlled, observer-blind, dose-finding, vaccine candidate-selection (Phase 1) and efficacy (Phase 2/3) study that has enrolled approximately 44,000 participants, 12 years of age or older. Of these, approximately 43,448 participants (21,720 Pfizer-BioNTech COVID-19 Vaccine; 21,728 placebo) in Phase 2/3 are 16 years of age or older (including 138 and 145 adolescents 16 and 17 years of age in the vaccine and placebo groups, respectively).

At the time of the analysis of Study 2 for the EUA, 37,586 (18,801 Pfizer-BioNTech COVID-19 Vaccine and 18,785 placebo) participants 16 years of age or older have been followed for a median of 2 months after the second dose of Pfizer-BioNTech COVID-19 Vaccine.

The safety evaluation in Study 2 is ongoing. The safety population includes participants enrolled by October 9, 2020, and includes safety data accrued through November 14, 2020. Participants 18 years and older in the reactogenicity subset are monitored for solicited local and systemic reactions and use of antipyretic medication after each vaccination in an electronic diary. Participants are being monitored for unsolicited adverse events, including serious adverse events, throughout the study [from Dose 1 through 1 month (all unsolicited adverse events) or 6 months (serious adverse events) after the last vaccination].

Demographic characteristics in Study 2 were generally similar with regard to age, gender, race, and ethnicity among participants who received Pfizer-BioNTech COVID-19 Vaccine and those who received placebo. Overall, among the total participants who received either the Pfizer-BioNTech COVID-19 Vaccine or placebo, 50.6% were male and 49.4% were female, 83.1% were White, 9.1% were Black or African American, 28.0% were Hispanic/Latino, 4.3% were Asian, and 0.5% were American Indian/Alaska Native.

Local and Systemic Adverse Reactions Solicited in the Study 2

Table 1 and Table 2 present the frequency and severity of solicited local and systemic reactions, respectively, within 7 days following each dose of Pfizer-BioNTech COVID-19 Vaccine and placebo in the subset of participants 18 to 55 years of age included in the EUA safety population who were monitored for reactogenicity with an electronic diary.

Table 3 and Table 4 present the frequency and severity of reported solicited local and systemic reactions, respectively, within 7 days of each dose of Pfizer-BioNTech COVID-19 Vaccine and placebo for participants 56 years of age and older.

Across both age groups, the mean duration of pain at the injection site after Dose 2 was 2.5 days (range 1 to 36 days), for redness 2.6 days (range 1 to 34 days), and for swelling 2.3 days (range 1 to 34 days) for participants in the Pfizer-BioNTech COVID-19 Vaccine group.

Solicited reactogenicity data in 16 and 17 year-old participants are limited.

Table 1: Study 2 – Frequency and Percentages of Participants with Solicited Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Participants 18-55 Years of Age‡ – Reactogenicity Subset of the Safety Population*

	Pfizer-BioNTech COVID-19 Vaccine Dose 1 N[a]=2291 n[b] (%)	Placebo Dose 1 N[a]=2298 n[b] (%)	Pfizer-BioNTech COVID-19 Vaccine Dose 2 N[a]=2098 n[b] (%)	Placebo Dose 2 N[a]=2103 n[b] (%)
Redness[c]				
Any (>2 cm)	104 (4.5)	26 (1.1)	123 (5.9)	14 (0.7)
Mild	70 (3.1)	16 (0.7)	73 (3.5)	8 (0.4)
Moderate	28 (1.2)	6 (0.3)	40 (1.9)	6 (0.3)
Severe	6 (0.3)	4 (0.2)	10 (0.5)	0 (0.0)
Swelling[c]				
Any (>2 cm)	132 (5.8)	11 (0.5)	132 (6.3)	5 (0.2)
Mild	88 (3.8)	3 (0.1)	80 (3.8)	3 (0.1)
Moderate	39 (1.7)	5 (0.2)	45 (2.1)	2 (0.1)
Severe	5 (0.2)	3 (0.1)	7 (0.3)	0 (0.0)
Pain at the injection site[d]				
Any	1904 (83.1)	322 (14.0)	1632 (77.8)	245 (11.7)
Mild	1170 (51.1)	308 (13.4)	1039 (49.5)	225 (10.7)
Moderate	710 (31.0)	12 (0.5)	568 (27.1)	20 (1.0)
Severe	24 (1.0)	2 (0.1)	25 (1.2)	0 (0.0)

Note: Reactions were collected in the electronic diary (e-diary) from Day 1 to Day 7 after vaccination.
a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.
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.
‡ Eight participants were between 16 and 17 years of age.
* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.

Table 2: Study 2 – Frequency and Percentages of Participants with Solicited Systemic Reactions, by Maximum Severity, Within 7 Days After Each Dose – Participants 18-55 Years of Age‡ – Safety Population*

	Pfizer-BioNTech COVID-19 Vaccine Dose 1 N[a]=2291 n[b] (%)	Placebo Dose 1 N[a]=2298 n[b] (%)	Pfizer-BioNTech COVID-19 Vaccine Dose 2 N[a]=2098 n[b] (%)	Placebo Dose 2 N[a]=2103 n[b] (%)
Fever				
≥38.0°C	85 (3.7)	20 (0.9)	331 (15.8)	10 (0.5)
≥38.0°C to 38.4°C	64 (2.8)	10 (0.4)	194 (9.2)	5 (0.2)
>38.4°C to 38.9°C	15 (0.7)	5 (0.2)	110 (5.2)	3 (0.1)
>38.9°C to 40.0°C	6 (0.3)	3 (0.1)	26 (1.2)	2 (0.1)
>40.0°C	0 (0.0)	2 (0.1)	1 (0.0)	0 (0.0)
Fatigue[c]				
Any	1085 (47.4)	767 (33.4)	1247 (59.4)	479 (22.8)
Mild	597 (26.1)	467 (20.3)	442 (21.1)	248 (11.8)
Moderate	455 (19.9)	289 (12.6)	708 (33.7)	217 (10.3)
Severe	33 (1.4)	11 (0.5)	97 (4.6)	14 (0.7)

	Pfizer-BioNTech COVID-19 Vaccine Dose 1 N[a]=2291 n[b] (%)	Placebo Dose 1 N[a]=2298 n[b] (%)	Pfizer-BioNTech COVID-19 Vaccine Dose 2 N[a]=2098 n[b] (%)	Placebo Dose 2 N[a]=2103 n[b] (%)
Headache[c]				
Any	959 (41.9)	775 (33.7)	1085 (51.7)	506 (24.1)
Mild	628 (27.4)	505 (22.0)	538 (25.6)	321 (15.3)
Moderate	308 (13.4)	251 (10.9)	480 (22.9)	170 (8.1)
Severe	23 (1.0)	19 (0.8)	67 (3.2)	15 (0.7)
Chills[c]				
Any	321 (14.0)	146 (6.4)	737 (35.1)	79 (3.8)
Mild	230 (10.0)	111 (4.8)	359 (17.1)	65 (3.1)
Moderate	82 (3.6)	33 (1.4)	333 (15.9)	14 (0.7)
Severe	9 (0.4)	2 (0.1)	45 (2.1)	0 (0.0)
Vomiting[d]				
Any	28 (1.2)	28 (1.2)	40 (1.9)	25 (1.2)
Mild	24 (1.0)	22 (1.0)	28 (1.3)	16 (0.8)
Moderate	4 (0.2)	5 (0.2)	8 (0.4)	9 (0.4)
Severe	0 (0.0)	1 (0.0)	4 (0.2)	0 (0.0)
Diarrhea[e]				
Any	255 (11.1)	270 (11.7)	219 (10.4)	177 (8.4)
Mild	206 (9.0)	217 (9.4)	179 (8.5)	144 (6.8)
Moderate	46 (2.0)	52 (2.3)	36 (1.7)	32 (1.5)
Severe	3 (0.1)	1 (0.0)	4 (0.2)	1 (0.0)
New or worsened muscle pain[c]				
Any	487 (21.3)	249 (10.8)	783 (37.3)	173 (8.2)
Mild	256 (11.2)	175 (7.6)	326 (15.5)	111 (5.3)
Moderate	218 (9.5)	72 (3.1)	410 (19.5)	59 (2.8)
Severe	13 (0.6)	2 (0.1)	47 (2.2)	3 (0.1)
New or worsened joint pain[c]				
Any	251 (11.0)	138 (6.0)	459 (21.9)	109 (5.2)
Mild	147 (6.4)	95 (4.1)	205 (9.8)	54 (2.6)
Moderate	99 (4.3)	43 (1.9)	234 (11.2)	51 (2.4)
Severe	5 (0.2)	0 (0.0)	20 (1.0)	4 (0.2)
Use of antipyretic or pain medication[f]	638 (27.8)	332 (14.4)	945 (45.0)	266 (12.6)

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

a. N = Number of participants reporting at least 1 yes or no response for the specified event after the specified dose.
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.

‡ Eight participants were between 16 and 17 years of age.
* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.

Table 3: Study 2 – Frequency and Percentages of Participants with Solicited Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Participants 56 Years of Age and Older – Safety Population*

	Pfizer-BioNTech COVID-19 Vaccine Dose 1 N[a]=1802 n[b] (%)	Placebo Dose 1 N[a]=1792 n[b] (%)	Pfizer-BioNTech COVID-19 Vaccine Dose 2 N[a]=1660 n[b] (%)	Placebo Dose 2 N[a]=1646 n[b] (%)
Redness[c]				
Any (>2 cm)	85 (4.7)	19 (1.1)	120 (7.2)	12 (0.7)
Mild	55 (3.1)	12 (0.7)	59 (3.6)	8 (0.5)
Moderate	27 (1.5)	5 (0.3)	53 (3.2)	3 (0.2)
Severe	3 (0.2)	2 (0.1)	8 (0.5)	1 (0.1)
Swelling[c]				
Any (>2 cm)	118 (6.5)	21 (1.2)	124 (7.5)	11 (0.7)
Mild	71 (3.9)	10 (0.6)	68 (4.1)	5 (0.3)
Moderate	45 (2.5)	11 (0.6)	53 (3.2)	5 (0.3)
Severe	2 (0.1)	0 (0.0)	3 (0.2)	1 (0.1)
Pain at the injection site[d]				
Any (>2 cm)	1282 (71.1)	166 (9.3)	1098 (66.1)	127 (7.7)
Mild	1008 (55.9)	160 (8.9)	792 (47.7)	125 (7.6)
Moderate	270 (15.0)	6 (0.3)	298 (18.0)	2 (0.1)
Severe	4 (0.2)	0 (0.0)	8 (0.5)	0 (0.0)

Note: Reactions were collected in the electronic diary (e-diary) from Day 1 to Day 7 after vaccination.
a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.
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.
* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.

Table 4: Study 2 – Frequency and Percentages of Participants with Solicited Systemic Reactions, by Maximum Severity, Within 7 Days After Each Dose – Participants 56 Years of Age and Older – Reactogenicity Subset of the Safety Population*

	Pfizer-BioNTech COVID-19 Vaccine Dose 1 N[a]=1802 n[b] (%)	Placebo Dose 1 N[a]=1792 n[b] (%)	Pfizer-BioNTech COVID-19 Vaccine Dose 2 N[a]=1660 n[b] (%)	Placebo Dose 2 N[a]=1646 n[b] (%)
Fever				
≥38.0°C	26 (1.4)	7 (0.4)	181 (10.9)	4 (0.2)
≥38.0°C to 38.4°C	23 (1.3)	2 (0.1)	131 (7.9)	2 (0.1)
>38.4°C to 38.9°C	1 (0.1)	3 (0.2)	45 (2.7)	1 (0.1)
>38.9°C to 40.0°C	1 (0.1)	2 (0.1)	5 (0.3)	1 (0.1)
>40.0°C	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue[c]				
Any	615 (34.1)	405 (22.6)	839 (50.5)	277 (16.8)
Mild	373 (20.7)	252 (14.1)	351 (21.1)	161 (9.8)
Moderate	240 (13.3)	150 (8.4)	442 (26.6)	114 (6.9)
Severe	2 (0.1)	3 (0.2)	46 (2.8)	2 (0.1)

	Pfizer-BioNTech COVID-19 Vaccine Dose 1 N[a]=1802 n[b] (%)	Placebo Dose 1 N[a]=1792 n[b] (%)	Pfizer-BioNTech COVID-19 Vaccine Dose 2 N[a]=1660 n[b] (%)	Placebo Dose 2 N[a]=1646 n[b] (%)
Headache[c]				
Any	454 (25.2)	325 (18.1)	647 (39.0)	229 (13.9)
Mild	348 (19.3)	242 (13.5)	422 (25.4)	165 (10.0)
Moderate	104 (5.8)	80 (4.5)	216 (13.0)	60 (3.6)
Severe	2 (0.1)	3 (0.2)	9 (0.5)	4 (0.2)
Chills[c]				
Any	113 (6.3)	57 (3.2)	377 (22.7)	46 (2.8)
Mild	87 (4.8)	40 (2.2)	199 (12.0)	35 (2.1)
Moderate	26 (1.4)	16 (0.9)	161 (9.7)	11 (0.7)
Severe	0 (0.0)	1 (0.1)	17 (1.0)	0 (0.0)
Vomiting[d]				
Any	9 (0.5)	9 (0.5)	11 (0.7)	5 (0.3)
Mild	8 (0.4)	9 (0.5)	9 (0.5)	5 (0.3)
Moderate	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)
Severe	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Diarrhea[e]				
Any	147 (8.2)	118 (6.6)	137 (8.3)	99 (6.0)
Mild	118 (6.5)	100 (5.6)	114 (6.9)	73 (4.4)
Moderate	26 (1.4)	17 (0.9)	21 (1.3)	22 (1.3)
Severe	3 (0.2)	1 (0.1)	2 (0.1)	4 (0.2)
New or worsened muscle pain[c]				
Any	251 (13.9)	149 (8.3)	477 (28.7)	87 (5.3)
Mild	168 (9.3)	100 (5.6)	202 (12.2)	57 (3.5)
Moderate	82 (4.6)	46 (2.6)	259 (15.6)	29 (1.8)
Severe	1 (0.1)	3 (0.2)	16 (1.0)	1 (0.1)
New or worsened joint pain[c]				
Any	155 (8.6)	109 (6.1)	313 (18.9)	61 (3.7)
Mild	101 (5.6)	68 (3.8)	161 (9.7)	35 (2.1)
Moderate	52 (2.9)	40 (2.2)	145 (8.7)	25 (1.5)
Severe	2 (0.1)	1 (0.1)	7 (0.4)	1 (0.1)
Use of antipyretic or pain medication	358 (19.9)	213 (11.9)	625 (37.7)	161 (9.8)

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

a. N = Number of participants reporting at least 1 yes or no response for the specified event after the specified dose.
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.
* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.

Unsolicited Adverse Events

Serious Adverse Events

In Study 2, among participants 16 to 55 years of age who had received at least 1 dose of vaccine or placebo (Pfizer-BioNTech COVID-19 Vaccine = 10,841; placebo = 10,851), serious adverse events from Dose 1 through up to 30 days after Dose 2 in ongoing follow-up were reported by 0.4% of Pfizer-BioNTech COVID-19 Vaccine recipients and by 0.3% of placebo recipients. In a similar analysis, in participants 56 years of age and older (Pfizer-BioNTech COVID-19 Vaccine = 7960, placebo = 7934), serious adverse events were reported by 0.8% of Pfizer-BioNTech COVID-19 Vaccine recipients and by 0.6% of placebo recipients who received at least 1 dose of Pfizer-BioNTech COVID-19 Vaccine or placebo, respectively. In these analyses, 91.6% of study participants had at least 30 days of follow-up after Dose 2. Appendicitis was reported as a serious adverse event for 12 participants, and numerically higher in the vaccine group, 8 vaccine participants and 4 placebo participants. Currently available information is insufficient to determine a causal relationship with the vaccine. There were no other notable patterns or numerical imbalances between treatment groups for specific categories of serious adverse events (including neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to Pfizer-BioNTech COVID-19 Vaccine.

Non-Serious Adverse Events

Overall in Study 2 in which 10,841 participants 16 to 55 years of age received Pfizer-BioNTech COVID-19 Vaccine and 10,851 participants received placebo, non-serious adverse events from Dose 1 through up to 30 days after Dose 2 in ongoing follow-up were reported in 29.3% of participants who received Pfizer-BioNTech COVID-19 Vaccine and 13.2% of participants in the placebo group, for participants who received at least 1 dose. Overall in a similar analysis in which 7960 participants 56 years of age and older received Pfizer-BioNTech COVID-19 Vaccine, non-serious adverse events within 30 days were reported in 23.8% of participants who received Pfizer-BioNTech COVID-19 Vaccine and 11.7% of participants in the placebo group, for participants who received at least 1 dose. In these analyses, 91.6% of study participants had at least 30 days of follow-up after Dose 2. The higher frequency of reported unsolicited non-serious adverse events among Pfizer BioNTech COVID-19 Vaccine recipients compared to placebo recipients was primarily attributed to local and systemic adverse events reported during the first 7 days following vaccination that are consistent with adverse reactions solicited among participants in the reactogenicity subset and presented in Tables 3 and 4. From Dose 1 through 30 days after Dose 2, reports of lymphadenopathy were imbalanced with notably more cases in the Pfizer-BioNTech COVID-19 Vaccine group (64) vs. the placebo group (6), which is plausibly related to vaccination. Throughout the safety follow-up period to date, Bell's palsy (facial paralysis) was reported by four participants in the Pfizer-BioNTech COVID-19 Vaccine group. Onset of facial paralysis was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of Bell's palsy were reported in the placebo group. Currently available information is insufficient to determine a causal relationship with the vaccine. There were no other notable patterns or numerical imbalances between treatment groups for specific categories of non-serious adverse events (including other neurologic or neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to Pfizer-BioNTech COVID-19 Vaccine.

8 REQUIREMENTS AND INSTRUCTIONS FOR REPORTING ADVERSE EVENTS AND VACCINE ADMINISTRATION ERRORS

See Overall Safety Summary (Section 6) for additional information.

The vaccination provider enrolled in the federal COVID-19 Vaccination Program is responsible for MANDATORY reporting of the listed events following Pfizer-BioNTech COVID-19 Vaccine to the Vaccine Adverse Event Reporting System (VAERS):

- Vaccine administration errors whether or not associated with an adverse event
- Serious adverse events* (irrespective of attribution to vaccination)
- Cases of Multisystem Inflammatory Syndrome (MIS) in children and adults
- Cases of COVID-19 that result in hospitalization or death

*Serious adverse events are defined as:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- An important medical event that based on appropriate medical judgement may jeopardize the individual and may require medical or surgical intervention to prevent one of the outcomes listed above

Instructions for Reporting to VAERS

The vaccination provider enrolled in the federal COVID-19 Vaccination Program should complete and submit a VAERS form to FDA using one of the following methods:

- Complete and submit the report online: https://vaers.hhs.gov/reportevent.html, or
- If you are unable to submit this form electronically, you may fax it to VAERS at 1-877-721-0366. If you need additional help submitting a report you may call the VAERS toll-free information line at 1-800-822-7967 or send an email to info@vaers.org.

IMPORTANT: When reporting adverse events or vaccine administration errors to VAERS, please complete the entire form with detailed information. It is important that the information reported to FDA be as detailed and complete as possible. Information to include:

- Patient demographics (e.g., patient name, date of birth)
- Pertinent medical history
- Pertinent details regarding admission and course of illness
- Concomitant medications
- Timing of adverse event(s) in relationship to administration of the Pfizer-BioNTech COVID-19 Vaccine
- Pertinent laboratory and virology information
- Outcome of the event and any additional follow-up information if it is available at the time of the VAERS report. Subsequent reporting of follow-up information should be completed if additional details become available.

The following steps are highlighted to provide the necessary information for safety tracking:

1. In Box 17, provide information on Pfizer-BioNTech COVID-19 Vaccine and any other vaccines administered on the same day; and in Box 22, provide information on any other vaccines received within one month prior.
2. In Box 18, description of the event:
    a. Write "Pfizer-BioNTech COVID-19 Vaccine EUA" as the first line.
    b. Provide a detailed report of vaccine administration error and/or adverse event. It is important to provide detailed information regarding the patient and adverse event/medication error for ongoing safety evaluation of this unapproved vaccine. Please see information to include listed above.

3. Contact information:
    a. In Box 13, provide the name and contact information of the prescribing healthcare provider or institutional designee who is responsible for the report.
    b. In Box 14, provide the name and contact information of the best doctor/healthcare professional to contact about the adverse event.
    c. In Box 15, provide the address of the facility where vaccine was given (NOT the healthcare provider's office address).

Other Reporting Instructions

Vaccination providers may report to VAERS other adverse events that are not required to be reported using the contact information above.

To the extent feasible, report adverse events to Pfizer Inc. using the contact information below or by providing a copy of the VAERS form to Pfizer Inc.

Website	Fax number	Telephone number
www.pfizersafetyreporting.com	1-866-635-8337	1-800-438-1985

10 DRUG INTERACTIONS

There are no data to assess the concomitant administration of the Pfizer-BioNTech COVID-19 Vaccine with other vaccines.

11 USE IN SPECIFIC POPULATIONS

11.1 Pregnancy

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Available data on Pfizer-BioNTech COVID-19 Vaccine administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

11.2 Lactation

Risk Summary

Data are not available to assess the effects of Pfizer-BioNTech COVID-19 Vaccine on the breastfed infant or on milk production/excretion.

11.3 Pediatric Use

Emergency Use Authorization of Pfizer-BioNTech COVID-19 Vaccine in adolescents 16 and 17 years of age is based on extrapolation of safety and effectiveness from adults 18 years of age and older. Emergency Use Authorization of Pfizer BioNTech COVID-19 Vaccine does not include use in individuals younger than 16 years of age.

11.4 Geriatric Use

Clinical studies of Pfizer-BioNTech COVID-19 Vaccine include participants 65 years of age and older and their data contributes to the overall assessment of safety and efficacy *[see Overall Safety Summary (6.1) and Clinical Trial Results and Supporting Data for EUA (18.1)]*. Of the total number of Pfizer-BioNTech COVID-19 Vaccine recipients in Study 2 (N=20,033), 21.4% (n=4,294) were 65 years of age and older and 4.3% (n=860) were 75 years of age and older.

13 DESCRIPTION

The Pfizer-BioNTech COVID-19 Vaccine is supplied as a frozen suspension in multiple dose vials; each vial must be diluted with 1.8 mL of sterile 0.9% Sodium Chloride Injection, USP prior to use to form the vaccine. Each dose of the Pfizer-BioNTech COVID-19 Vaccine contains 30 mcg of a nucleoside-modified messenger RNA (modRNA) encoding the viral spike (S) glycoprotein of SARS-CoV-2.

Each dose of the Pfizer-BioNTech COVID-19 Vaccine also includes the following ingredients: lipids (0.43 mg (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 0.05 mg 2[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 0.09 mg 1,2-distearoyl-sn-glycero-3-phosphocholine, and 0.2 mg cholesterol), 0.01 mg potassium chloride, 0.01 mg monobasic potassium phosphate, 0.36 mg sodium chloride, 0.07 mg dibasic sodium phosphate dihydrate, and 6 mg sucrose. The diluent (0.9% Sodium Chloride Injection, USP) contributes an additional 2.16 mg sodium chloride per dose.

The Pfizer-BioNTech COVID-19 Vaccine does not contain preservative. The vial stoppers are not made with natural rubber latex.

14 CLINICAL PHARMACOLOGY

14.1 Mechanism of Action

The modRNA in the Pfizer-BioNTech COVID-19 Vaccine is formulated in lipid particles, which enable delivery of the RNA into host cells to allow expression of the SARS-CoV-2 S antigen. The vaccine elicits an immune response to the S antigen, which protects against COVID-19.

18 CLINICAL TRIAL RESULTS AND SUPPORTING DATA FOR EUA

18.1 Efficacy in Participants 16 Years of Age and Older

Study 2 is a multicenter, multinational, Phase 1/2/3, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate–selection, and efficacy study in participants 12 years of age and older. Randomization was stratified by age: 12 through 15 years of age, 16 through 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥56-year stratum. The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19. Participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, were included as were participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV).

In the Phase 2/3 portion approximately 44,000 participants 12 years of age and older were randomized equally and received 2 doses of Pfizer-BioNTech COVID-19 Vaccine or placebo separated by 21 days. Participants are planned to be followed for up to 24 months, for assessments of safety and efficacy against COVID-19.

The population for the analysis of the primary efficacy endpoint included, 36,621 participants 12 years of age and older (18,242 in the Pfizer-BioNTech COVID-19 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. Table 5 presents the specific demographic characteristics in the studied population.

Table 5: Demographics (population for the primary efficacy endpoint)[a]

	Pfizer-BioNTech COVID-19 Vaccine (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 through 15 years	46 (0.3)	42 (0.2)
≥16 through 17 years	66 (0.4)	68 (0.4)
≥16 through 64 years	14,216 (77.9)	14,299 (77.8)
≥65 through 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 disease
- 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)

Efficacy Against COVID-19

The population in the primary efficacy analysis included all participants 12 years of age and older who had been enrolled from July 27, 2020, and followed for the development of COVID-19 through November 14, 2020. Participants 18 to 55 years of age and 56 years of age and older began enrollment from July 27,2020, 16 to 17 years of age began enrollment from September 16, 2020 and 12 to 15 years of age began enrollment from October 15, 2020.

The 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

First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection*			
Subgroup	**Pfizer-BioNTech COVID-19 Vaccine 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 subjects[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 and older	1 0.508 (3848)	19 0.511 (3880)	94.7 (66.7, 99.9)[g]
First COVID-19 occurrence from 7 days after Dose 2 in participants with or without evidence of prior SARS-CoV-2 infection			
Subgroup	**Pfizer-BioNTech COVID-19 Vaccine 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 subjects[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 and older	1 0.530 (4044)	19 0.532 (4067)	94.7 (66.8, 99.9)[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).

* 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 participants 12 to 15 years of age.
f. Credible interval for VE was calculated using a beta-binomial model with a beta (0.700102, 1) prior for θ=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. Confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.

19 HOW SUPPLIED/STORAGE AND HANDLING

Pfizer-BioNTech COVID-19 Vaccine Suspension for Intramuscular Injection, Multiple Dose Vials are supplied in a carton containing 25 multiple dose vials (NDC 59267-1000-3) or 195 multiple dose vials (NDC 59267-1000-2). After dilution, one vial contains 6 doses of 0.3 mL. Vial labels and cartons may state that after dilution, a vial contains 5 doses of 0.3 mL. The information in this Full EUA Prescribing Information regarding the number of doses per vial after dilution supersedes the number of doses stated on vial labels and cartons.

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

Do not refreeze thawed vials.

Frozen Vials Prior to Use

Cartons of Pfizer-BioNTech COVID-19 Vaccine Multiple Dose Vials arrive in thermal containers with dry ice. Once received, remove the vial cartons immediately from the thermal container and store in an ultra-low temperature freezer between -80°C to -60°C (-112°F to -76°F). Vials must be kept frozen between -80°C to -60°C (-112°F to -76°F) and protected from light, in the original cartons, until ready to use.

If an ultra-low temperature freezer is not available, the thermal container in which the Pfizer-BioNTech COVID-19 Vaccine arrives may be used as temporary storage when consistently re-filled to the top of the container with dry ice. Refer to the re-icing guidelines packed in the original thermal container for instructions regarding the use of the thermal container for temporary storage. The thermal container maintains a temperature range of -90°C to -60°C (-130°F to -76°F). Storage of the vials between -96°C to -60°C (-141°F to -76°F) is not considered an excursion from the recommended storage condition.

Thawed Vials Before Dilution

Thawed Under Refrigeration
Thaw and then store undiluted vials in the refrigerator [2°C to 8°C (35°F to 46°F)] for up to 5 days (120 hours). A carton of 25 vials or 195 vials may take up to 2 or 3 hours, respectively, to thaw in the refrigerator, whereas a fewer number of vials will thaw in less time.

Transportation at 2°C to 8°C (35°F to 46°F)
If local redistribution is needed and full cartons containing vials cannot be transported at -90°C to -60°C (-130°F to -76°F), available data support transportation of one or more thawed vials at 2°C to 8°C (35°F to 46°F) for up to 12 hours. Any hours used for transport at 2°C to 8°C (35°F to 46°F) count against the 120-hour limit for storage at 2°C to 8°C (35°F to 46°F).

Thawed at Room Temperature
For immediate use, thaw undiluted vials at room temperature [up to 25°C (77°F)] for 30 minutes. Thawed vials can be handled in room light conditions.

Vials must reach room temperature before dilution.

Undiluted vials may be stored at room temperature for no more than 2 hours.

Vials After Dilution

After dilution, store vials between 2°C to 25°C (35°F to 77°F) and use within 6 hours from the time of dilution. During storage, minimize exposure to room light, and avoid exposure to direct sunlight and ultraviolet light. Any vaccine remaining in vials must be discarded after 6 hours. Do not refreeze.

20 PATIENT COUNSELING INFORMATION

Advise the recipient or caregiver to read the Fact Sheet for Recipients and Caregivers.

The vaccination provider must include vaccination information in the state/local jurisdiction's Immunization Information System (IIS) or other designated system. Advise recipient or caregiver that more information about IISs can be found at: https://www.cdc.gov/vaccines/programs/iis/about.html.

21 CONTACT INFORMATION

For general questions, visit the website or call the telephone number provided below.

Website	Telephone number
www.cvdvaccine.com	1-877-829-2619 (1-877-VAX-CO19)

This Full EUA Prescribing Information may have been updated. For the most recent Full EUA Prescribing Information, please see www.cvdvaccine.com.

Manufactured by
Pfizer Inc., New York, NY 10017

Manufactured for
BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

LAB-1457-5.0

Revised: January 2021

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Comirnaty concentrate for dispersion for injection
COVID-19 mRNA Vaccine (nucleoside modified)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

One vial (0.45 mL) contains 5 doses of 0.3 mL after dilution.

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

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 SARS-CoV-2.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for dispersion for injection (sterile concentrate).
The vaccine is a white to off-white frozen dispersion (pH: 6.9 - 7.9).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Comirnaty is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 16 years of age and older.

The use of this vaccine should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Individuals 16 years of age and older
Comirnaty is administered intramuscularly after dilution as a course of 2 doses (0.3 mL each) at least 21 days apart (see sections 4.4 and 5.1).

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

Paediatric population
The safety and efficacy of Comirnaty in children and adolescents aged less than 16 years of age have not yet been established. Limited data are available.

Elderly population
No dosage adjustment is required in elderly individuals ≥ 65 years of age.

Method of administration

Comirnaty should be administered intramuscularly.

The preferred site is the deltoid muscle of the upper arm.

Do not inject the vaccine intravascularly, subcutaneously or intradermally.

The vaccine should not be mixed in the same syringe with any other vaccines or medicinal products.

For precautions to be taken before administering the vaccine, see section 4.4.

For instructions regarding thawing, handling and disposal of the vaccine, 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

Hypersensitivity and anaphylaxis

Events of anaphylaxis have been reported. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine.

Close observation for at least 15 minutes is recommended following vaccination. A second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose of Comirnaty.

Anxiety-related reactions

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions may occur in association with vaccination as a psychogenic response to the needle injection. It is important that precautions are in place to avoid injury from fainting.

Concurrent illness

Vaccination should be postponed in individuals suffering from acute severe febrile illness or acute infection. The presence of a minor infection and/or low-grade fever should not delay vaccination.

Thrombocytopenia and coagulation disorders

As with other intramuscular injections, the vaccine should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia) because bleeding or bruising may occur following an intramuscular administration in these individuals.

Immunocompromised individuals

The efficacy, safety and immunogenicity of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of Comirnaty may be lower in immunosuppressed individuals.

Duration of protection

The duration of protection afforded by the vaccine is unknown as it is still being determined by ongoing clinical trials.

Limitations of vaccine effectiveness

As with any vaccine, vaccination with Comirnaty may not protect all vaccine recipients. Individuals may not be fully protected until 7 days after their second dose of vaccine.

Excipients:

This vaccine contains less than 1 mmol potassium (39 mg) per dose, that is to say essentially 'potassium-free'.

This vaccine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concomitant administration of Comirnaty with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is limited experience with use of Comirnaty in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development (see section 5.3). Administration of Comirnaty in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and foetus.

Breast-feeding

It is unknown whether Comirnaty is excreted in human milk.

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3)

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of safety profile

The safety of Comirnaty was evaluated in participants 16 years of age and older in 2 clinical studies that included 21,744 participants that have received at least one dose of Comirnaty.

In Study 2, a total of 21,720 participants 16 years of age or older received at least 1 dose of Comirnaty and a total of 21,728 participants 16 years of age or older received placebo (including 138 and 145 adolescents 16 and 17 years of age in the vaccine and placebo groups, respectively). A total of 20,519 participants 16 years of age or older received 2 doses of Comirnaty.

At the time of the analysis of Study 2, a total of 19,067 (9,531 Comirnaty and 9,536 placebo) participants 16 years of age or older were evaluated for safety for at least 2 months after the second dose of Comirnaty. This included a total of 10,727 (5,350 Comirnaty and 5,377 placebo) participants 16 to 55 years of age and a total of 8,340 (4,181 Comirnaty and 4,159 placebo) participants 56 years and older.

The most frequent adverse reactions in participants 16 years of age and older were injection site pain (> 80%), fatigue (> 60%), headache (> 50%), myalgia and 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. A slightly lower frequency of reactogenicity events was associated with greater age.

Tabulated list of adverse reactions from clinical studies
Adverse reactions observed during clinical studies are listed below according to the following frequency categories:

Very common (≥ 1/10),
Common (≥ 1/100 to < 1/10),
Uncommon (≥ 1/1,000 to < 1/100),
Rare (≥ 1/10,000 to < 1/1,000),
Very rare (< 1/10,000),
Not known (cannot be estimated from the available data).

Table 1: Adverse reactions from Comirnaty clinical trials

System Organ Class	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)	Not known (cannot be estimated from the available data)
Blood and lymphatic system disorders			Lymphadenopathy		
Immune system disorders					Anaphylaxis; hypersensitivity
Psychiatric disorders			Insomnia		

System Organ Class	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)	Not known (cannot be estimated from the available data)
Nervous system disorders	Headache			Acute peripheral facial paralysis†	
Gastrointestinal disorders		Nausea			
Musculoskeletal and connective tissue disorders	Arthralgia; myalgia		Pain in extremity		
General disorders and administration site conditions	Injection site pain; fatigue; chills; pyrexia*; injection site swelling	Injection site redness	Malaise; injection site pruritus		

*A higher frequency of pyrexia was observed after the 2nd dose.
†Throughout the safety follow-up period to date, acute peripheral facial paralysis (or palsy) was reported by four participants in the COVID-19 mRNA Vaccine group. Onset was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.

The safety profile in 545 subjects receiving Comirnaty, that were seropositive for SARS-CoV-2 at baseline, was similar to that seen in the general population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V and include batch/Lot number if available.

4.9 Overdose

Overdose data is available from 52 study participants included in the clinical trial that due to an error in dilution received 58 micrograms of Comirnaty. The vaccine recipients did not report an increase in reactogenicity or adverse reactions.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vaccines, ATC code: J07BX

Mechanism of action

The nucleoside-modified messenger RNA in Comirnaty is formulated in lipid nanoparticles, which enable delivery of the non replicating RNA into host cells to direct transient expression of the SARS-CoV-2 S antigen. The mRNA codes for membrane-anchored, full-length S with two point mutations within the central helix. Mutation of these two amino acids to proline locks S in an antigenically preferred prefusion conformation. The vaccine elicits both neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19.

Efficacy

Study 2 is a multicentre, multinational, Phase 1/2/3 randomised, placebo-controlled, observer-blind dose-finding, vaccine candidate selection and efficacy study in participants 12 years of age and older. Randomisation was stratified by age: 12 through 15 years of age, 16 through 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥ 56-year stratum. The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19. Participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrolment, were included as were participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis B virus (HBV). At the time of the analysis of Study 2, information presented is based on participants 16 years and older.

Efficacy in participants 16 years of age and older

In the Phase 2/3 portion, approximately 44,000 participants were randomised equally and were to receive 2 doses of COVID-19 mRNA Vaccine or placebo separated by 21 days. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. Participants are planned to be followed for up to 24 months after Dose 2, for assessments of safety and efficacy against COVID-19. In the clinical study, participants were required to observe a minimum interval of 14 days before and after administration of an influenza vaccine in order to receive either placebo or COVID-19 mRNA Vaccine. In the clinical study, participants were required to observe a minimum interval of 60 days before or after receipt of blood/plasma products or immunoglobulins within through conclusion of the study in order to receive either placebo or COVID-19 mRNA Vaccine.

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. In addition, 134 participants were between the ages of 16 to 17 years of age (66 in the COVID-19 mRNA Vaccine group and 68 in the placebo group) and 1616 participants 75 years of age and older (804 in the COVID-19 mRNA Vaccine group and 812 in the placebo group).

Efficacy against COVID-19

At the time of the primary efficacy analysis, participants had been followed for symptomatic COVID-19 for in total 2,214 person-years for the COVID-19 mRNA Vaccine and in total 2,222 person-years in the placebo group.

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).

The vaccine efficacy information is presented in Table 2.

Table 2: Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants 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*			
Subgroup	**COVID-19 mRNA Vaccine 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)[f]
All subjects[e]	8 2.214 (17,411)	162 2.222 (17,511)	95.0 (90.0, 97.9)
16 to 64 years	7 1.706 (13,549)	143 1.710 (13,618)	95.1 (89.6, 98.1)
65 years and older	1 0.508 (3848)	19 0.511 (3880)	94.7 (66.7, 99.9)
65 to 74 years	1 0.406 (3074)	14 0.406 (3095)	92.9 (53.1, 99.8)
75 years and older	0 0.102 (774)	5 0.106 (785)	100.0 (-13.1, 100.0)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 [*Case definition: (at least 1 of) 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, diarrhoea or vomiting.]

* Participants 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 nucleic acid amplification tests (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 subjects 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 subjects at risk for the endpoint.
e. No confirmed cases were identified in participants 12 to 15 years of age.
f. Confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time. CI not adjusted for multiplicity.

In the second primary analysis, compared to placebo, efficacy of COVID-19 mRNA Vaccine in participants from first COVID-19 occurrence from 7 days after Dose 2 compared to participants with or without evidence of prior infection with SARS-CoV-2 was 94.6% (95% credible interval of 89.9% to 97.3%) in participants 16 years of age and older.

Additionally, subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across genders, racial and ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Comirnaty in the paediatric population in prevention of COVID-19 (see section 4.2 for information on paediatric use).

This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited. The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

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 reproductive and developmental toxicity.

General toxicity
Rats intramuscularly administered Comirnaty (receiving 3 full human doses once weekly, generating relatively higher levels in rats due to body weight differences) demonstrated some injection site oedema and erythema and increases in white blood cells (including basophils and eosinophils) consistent with an inflammatory response as well as vacuolation of portal hepatocytes without evidence of liver injury. All effects were reversible.

Genotoxicity/Carcinogenicity
Neither genotoxicity nor carcinogenicity studies were performed. The components of the vaccine (lipids and mRNA) are not expected to have genotoxic potential.

Reproductive toxicity
Reproductive and developmental toxicity were investigated in rats in a combined fertility and developmental toxicity study where female rats were intramuscularly administered Comirnaty prior to mating and during gestation (receiving 4 full human doses that generate relatively higher levels in rat due to body weight differences, spanning between pre-mating day 21 and gestational day 20). SARS-CoV-2 neutralizing antibody responses were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in foetuses and offspring. There were no vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development. No Comirnaty data are available on vaccine placental transfer or excretion in milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)
2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)
1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
Cholesterol
Potassium chloride
Potassium dihydrogen phosphate
Sodium chloride
Disodium phosphate dihydrate
Sucrose
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial: 6 months at -90 °C to -60 °C'.

Once removed from the freezer, the unopened vaccine can be stored for up to 5 days at 2 °C to 8 °C, and up to 2 hours at temperatures up to 30 °C, prior to use.

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

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

Diluted medicinal product

Chemical and physical in-use stability has been demonstrated for 6 hours at 2 ℃ to 30 ℃ 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

Store in a freezer at -90 °C to -60 °C.
Store in the original package in order to protect from light.
During storage, minimise exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.
Thawed vials can be handled in room light conditions.

When you are ready to thaw or use the vaccine

- Open-lid vial trays, or vial trays containing less than 195 vials removed from frozen storage (< -60 °C) may be at room temperature (< 25 °C) for up to 3 minutes to remove vials or for transfer between ultra-low-temperature environments.
- Once a vial is removed from the vial tray, it should be thawed for use.
- After vial trays are returned to frozen storage following room temperature exposure, they must remain in frozen storage for at least 2 hours before they can be removed again.

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

6.5 Nature and contents of container

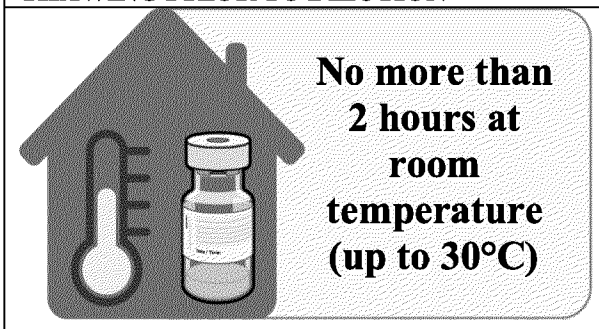
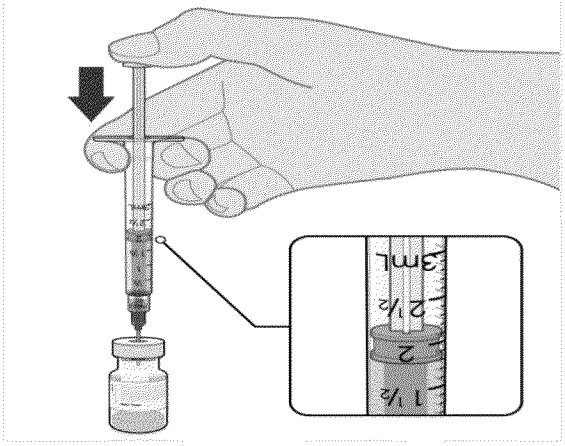
2 mL clear multidose vial (type I glass) with a stopper (synthetic bromobutyl rubber) and a flip-off plastic cap with aluminium seal. Each vial contains 5 doses.

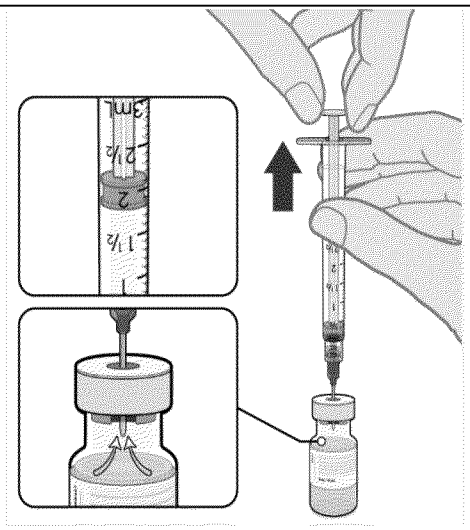
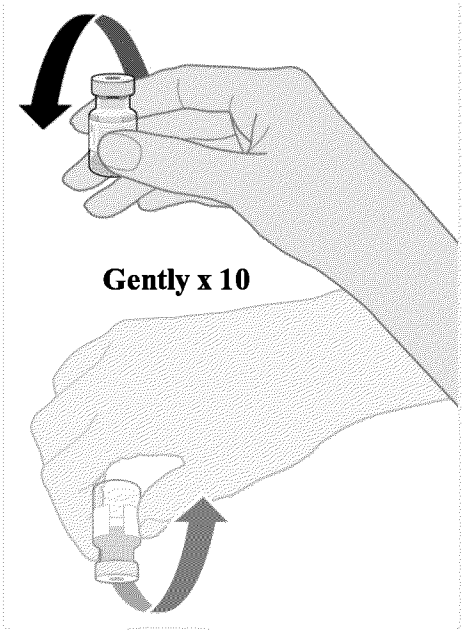
Pack size: 195 vials

6.6 Special precautions for disposal and other handling

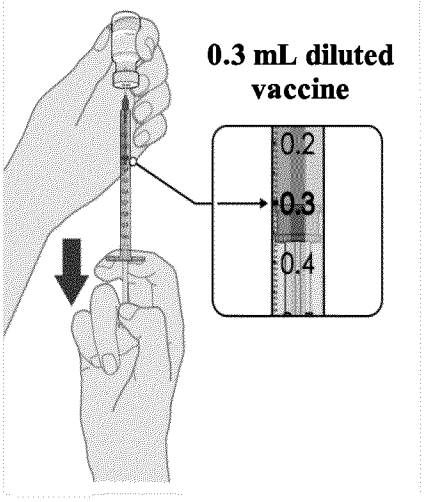
Handling instructions

Comirnaty 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. • 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**	• Equalise vial pressure before removing the needle from the vial stopper by withdrawing 1.8 mL air into the empty diluent syringe.
 **Gently x 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. Discard the diluted vaccine if particulates or discolouration are present.

<table>
<tr>
<td> 

Record appropriate date and time.
Use within 6 hours after dilution</td>
<td>• The diluted vials should be marked with the appropriate date and time.
• Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.</td>
</tr>
<tr>
<td colspan="2">PREPARATION OF INDIVIDUAL 0.3 mL DOSES OF COMIRNATY</td>
</tr>
<tr>
<td> 
</td>
<td>• After dilution, the vial contains 2.25 mL corresponding to 5 doses of 0.3 mL. Withdraw the required 0.3 mL dose of diluted vaccine using a sterile needle.
• Discard any unused vaccine within 6 hours after dilution.</td>
</tr>
</table>

Disposal

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

7. MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz
Germany
Phone: +49 6131 90840
Fax: +49 6131 9084390
info@biontech.de

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1528

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD month YYYY}

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCES AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCES AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance(s)
BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz
Germany

Rentschler Biopharma SE
Erwin-Rentschler-Strasse 21
88471 Laupheim
Germany

Wyeth BioPharma Division of Wyeth Pharmaceuticals LLC
1 Burtt Road
Andover, MA 01810
USA

Name and address of the manufacturers responsible for batch release
BioNTech Manufacturing GmbH
Kupferbergterrasse 17 - 19
55116 Mainz
Germany

Pfizer Manufacturing Belgium NV
Rijksweg 12
2870 Puurs
Belgium

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

In view of the declared Public Health Emergency of International Concern and in order to ensure early supply this medicinal product is subject to a time-limited exemption allowing reliance on batch control testing conducted in the registered site(s) that are located in a third country. This exemption ceases to be valid on 31 August 2021. Implementation of EU based batch control arrangements, including the necessary variations to the terms of the marketing authorisation, has to be completed by 31 August 2021 at the latest, in line with the agreed plan for this transfer of testing. Progress reports have to be submitted on 31 March 2021 and included in the annual renewal application.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

- **Official batch release**

In accordance with Article 114 of Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to complete the characterisation of the active substance and finished product, the MAH should provide additional data.	July 2021. Interim reports: 31 March 2021
In order to ensure consistent product quality, the MAH should provide additional information to enhance the control strategy, including the active substance and finished product specifications.	July 2021. Interim reports: March 2021
In order to confirm the consistency of the finished product manufacturing process, the MAH should provide additional validation data.	March 2021
In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional information about the synthetic process and control strategy for the excipient ALC-0315.	July 2021. Interim reports: January 2021, April 2021
In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional information about the synthetic process and control strategy for the excipient ALC-0159.	July 2021. Interim reports: January 2021, April 2021

Description	Due date
In order to confirm the efficacy and safety of Comirnaty, the MAH should submit the final Clinical Study Report for the randomized, placebo-controlled, observer-blind study C4591001.	December 2023

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON BOX LABEL

1. NAME OF THE MEDICINAL PRODUCT

COMIRNATY concentrate for dispersion for injection
COVID-19 mRNA Vaccine (nucleoside modified)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After dilution each vial contains 5 doses of 0.3 mL.

3. LIST OF EXCIPIENTS

Excipients: ALC-0315, ALC-0159, DSPC, cholesterol, potassium chloride, potassium dihydrogen phosphate, sodium chloride, disodium phosphate dihydrate, sucrose, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for dispersion for injection
195 multidose vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use after dilution.
Read the package leaflet before use.

Scan QR code for more information.

Dilute before use: Dilute each vial with 1.8 mL sodium chloride 9 mg/mL (0.9%) solution for injection.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Storage:
Prior to dilution, store at -90 °C to -60 °C in the original package in order to protect from light.
After dilution, store the vaccine at 2 °C to 30 °C and use within 6 hours. Discard any unused vaccine.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1528

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

COMIRNATY sterile concentrate
COVID-19 mRNA Vaccine
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 doses after dilution

6. OTHER

Discard date/time:

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Comirnaty concentrate for dispersion for injection
COVID-19 mRNA Vaccine (nucleoside modified)

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you receive this vaccine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Comirnaty is and what it is used for

Comirnaty is a vaccine used for preventing COVID-19 caused by SARS-CoV-2 virus.

Comirnaty is given to adults and adolescents from 16 years of age and older.

The vaccine causes the immune system (the body's natural defences) to produce antibodies and blood cells that work against the virus, so giving protection against COVID-19.

As Comirnaty does not contain the virus to produce immunity, it cannot give you COVID-19.

2. What you need to know before you receive Comirnaty

Comirnaty should not be given
- if you are allergic to the active substance or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions
Talk to your doctor, pharmacist or nurse before you are given the vaccine if:
- you have ever had a severe allergic reaction or breathing problems after any other vaccine injection or after you were given Comirnaty in the past.
- you have ever fainted following any needle injection.
- you have a severe illness or infection with high fever. However, you can have your vaccination if you have a mild fever or upper airway infection like a cold.
- you have a bleeding problem, you bruise easily or you use a medicine to prevent blood-clots.
- you have a weakened immune system, because of a disease such as HIV infection or a medicine such as corticosteroid that affects your immune system

As with any vaccine, the 2-dose vaccination course of Comirnaty may not fully protect all those who receive it and it is not known how long you will be protected.

Children and adolescents
Comirnaty is not recommended for children aged under 16 years.

Other medicines and Comirnaty
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines or have recently received any other vaccine.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before you receive this vaccine.

Driving and using machines
Some of the effects of vaccination mentioned in section 4 (Possible side effects) may temporarily affect your ability to drive or use machines. Wait until these effects have worn off before you drive or use machines.

Comirnaty contains potassium and sodium
This vaccine contains less than 1 mmol potassium (39 mg) per dose, that is to say essentially 'potassium-free'.

This vaccine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

3. How Comirnaty is given

Comirnaty is given after dilution as an injection of 0.3 mL into a muscle of your upper arm.

You will receive 2 injections, given at least 21 days apart.

After the first dose of Comirnaty, you should receive a second dose of the same vaccine after 21 days to complete the vaccination course.

If you have any further questions on the use of Comirnaty, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all vaccines, Comirnaty can cause side effects, although not everybody gets them.

Very common side effects: may affect more than 1 in 10 people
- injection site: pain, swelling
- tiredness
- headache
- muscle pain
- joint pain
- chills, fever

Common side effects: may affect up to 1 in 10 people
- injection site redness
- nausea

Uncommon side effects: may affect up to 1 in 100 people
- enlarged lymph nodes
- feeling unwell

- pain in limb
- insomnia
- injection site itching

Rare side effects: may affect up to 1 in 1,000 people
- temporary one sided facial drooping

Not known (cannot be estimated from the available data)
- severe allergic reaction

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V and include batch/Lot number if available. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Comirnaty

Keep this medicine out of the sight and reach of children.

The following information about storage, expiry and use and handling is intended for healthcare professionals.

Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.

Store in freezer at -90 °C to -60 °C.

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

After thawing, the vaccine should be diluted and used immediately. However, in-use stability data have demonstrated that once removed from freezer, the undiluted vaccine can be stored for up to 5 days at 2 °C to 8 °C, or up to 2 hours at temperatures up to 30 °C, prior to use.

After dilution, store the vaccine at 2 °C to 30 °C and use within 6 hours. Discard any unused vaccine.

Once removed from the freezer and diluted, the vials should be marked with the new discard date and time. Once thawed, the vaccine cannot be re-frozen.

Do not use this vaccine if you notice particulates in the dilution or discolouration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Comirnaty contains
- The active substance is COVID-19 mRNA Vaccine. After dilution, the vial contains 5 doses of 0.3 mL with 30 micrograms mRNA each.
- The other ingredients are:
  - ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)
  - 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)
  - 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
  - cholesterol

- potassium chloride
- potassium dihydrogen phosphate
- sodium chloride
- disodium phosphate dihydrate
- sucrose
- water for injections

What Comirnaty looks like and contents of the pack
The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9) provided in a multidose vial of 5 doses in a 2 mL clear vial (type I glass), with a rubber stopper and a flip-off plastic cap with aluminium seal.

Pack size: 195 vials

Marketing Authorisation Holder
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info@biontech.de

Manufacturers
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55116 Mainz
Germany

Pfizer Manufacturing Belgium NV
Rijksweg 12
2870 Puurs
Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Luxembourg/Luxemburg
Pfizer S.A./N.V.
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Pfizer Luxembourg SARL
Pfizer, podružnica za svetovanje s področja farmacevtske dejavnosti, Ljubljana
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Pfizer AB
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United Kingdom
Pfizer Limited
Tel: +44 (0) 1304 616161

This leaflet was last revised in

This medicine has been given 'conditional approval'. This means that there is more evidence to come about this medicine. The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Scan the code with a mobile device to get the package leaflet in different languages.

URL: www.comirnatyglobal.com

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

This package leaflet is available in all EU/EEA languages on the European Medicines Agency website.

The following information is intended for healthcare professionals only:

Administer Comirnaty intramuscularly after dilution as a course of 2 doses (0.3 mL each) at least 21 days apart.

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.

Handling instructions

- Comirnaty should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.
- 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.
- 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.
- 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.
- Equalise 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. Discard the diluted vaccine if particulates or discolouration are present.
- The diluted vials should be marked with the appropriate date and time.
- Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.
- After dilution, the vial contains 2.25 mL corresponding to 5 doses of 0.3 mL. Withdraw the required 0.3 mL dose of diluted vaccine using a sterile needle.
- 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.

Annex IV

Conclusions on the granting of the conditional marketing authorisation presented by the European Medicines Agency

Conclusions presented by the European Medicines Agency on:

- **Conditional marketing authorisation**

The CHMP having considered the application is of the opinion that the risk-benefit balance is favourable to recommend the granting of the conditional marketing authorisation as further explained in the European Public Assessment Report.

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Comirnaty concentrate for dispersion for injection
COVID-19 mRNA Vaccine (nucleoside modified)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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.

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

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 SARS-CoV-2.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for dispersion for injection (sterile concentrate).
The vaccine is a white to off-white frozen dispersion (pH: 6.9 - 7.9).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Comirnaty is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 16 years of age and older.

The use of this vaccine should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Individuals 16 years of age and older
Comirnaty is administered intramuscularly after dilution as a course of 2 doses (0.3 mL each) at least 21 days apart (see sections 4.4 and 5.1).

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

Paediatric population
The safety and efficacy of Comirnaty in children and adolescents aged less than 16 years of age have not yet been established. Limited data are available.

Elderly population
No dosage adjustment is required in elderly individuals ≥ 65 years of age.

Method of administration

Comirnaty should be administered intramuscularly after dilution (see section 6.6).

After dilution, vials of Comirnaty contain six doses of 0.3 mL of vaccine. In order to extract six doses from a single vial, low dead-volume syringes and/or needles should be used. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial. 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.

The preferred site is the deltoid muscle of the upper arm.

Do not inject the vaccine intravascularly, subcutaneously or intradermally.

The vaccine should not be mixed in the same syringe with any other vaccines or medicinal products.

For precautions to be taken before administering the vaccine, see section 4.4.

For instructions regarding thawing, handling and disposal of the vaccine, 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

Hypersensitivity and anaphylaxis

Events of anaphylaxis have been reported. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine.

Close observation for at least 15 minutes is recommended following vaccination. A second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose of Comirnaty.

Anxiety-related reactions

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions may occur in association with vaccination as a psychogenic response to the needle injection. It is important that precautions are in place to avoid injury from fainting.

Concurrent illness

Vaccination should be postponed in individuals suffering from acute severe febrile illness or acute infection. The presence of a minor infection and/or low-grade fever should not delay vaccination.

Thrombocytopenia and coagulation disorders

As with other intramuscular injections, the vaccine should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia) because bleeding or bruising may occur following an intramuscular administration in these individuals.

Immunocompromised individuals

The efficacy, safety and immunogenicity of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of Comirnaty may be lower in immunosuppressed individuals.

Duration of protection

The duration of protection afforded by the vaccine is unknown as it is still being determined by ongoing clinical trials.

Limitations of vaccine effectiveness

As with any vaccine, vaccination with Comirnaty may not protect all vaccine recipients. Individuals may not be fully protected until 7 days after their second dose of vaccine.

Excipients

This vaccine contains less than 1 mmol potassium (39 mg) per dose, that is to say essentially 'potassium-free'.

This vaccine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concomitant administration of Comirnaty with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is limited experience with use of Comirnaty in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development (see section 5.3). Administration of Comirnaty in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and foetus.

Breast-feeding

It is unknown whether Comirnaty is excreted in human milk.

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3)

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of safety profile

The safety of Comirnaty was evaluated in participants 16 years of age and older in 2 clinical studies that included 21,744 participants that have received at least one dose of Comirnaty.

In Study 2, a total of 21,720 participants 16 years of age or older received at least 1 dose of Comirnaty and a total of 21,728 participants 16 years of age or older received placebo (including 138 and 145 adolescents 16 and 17 years of age in the vaccine and placebo groups, respectively). A total of 20,519 participants 16 years of age or older received 2 doses of Comirnaty.

At the time of the analysis of Study 2, a total of 19,067 (9,531 Comirnaty and 9,536 placebo) participants 16 years of age or older were evaluated for safety for at least 2 months after the second dose of Comirnaty. This included a total of 10,727 (5,350 Comirnaty and 5,377 placebo) participants 16 to 55 years of age and a total of 8,340 (4,181 Comirnaty and 4,159 placebo) participants 56 years and older.

The most frequent adverse reactions in participants 16 years of age and older were injection site pain (> 80%), fatigue (> 60%), headache (> 50%), myalgia and 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. A slightly lower frequency of reactogenicity events was associated with greater age.

Tabulated list of adverse reactions from clinical studies

Adverse reactions observed during clinical studies are listed below according to the following frequency categories:

Very common (≥ 1/10),
Common (≥ 1/100 to < 1/10),
Uncommon (≥ 1/1,000 to < 1/100),
Rare (≥ 1/10,000 to < 1/1,000),
Very rare (< 1/10,000),
Not known (cannot be estimated from the available data).

Table 1: Adverse reactions from Comirnaty clinical trials

System Organ Class	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)	Not known (cannot be estimated from the available data)
Blood and lymphatic system disorders			Lymphadenopathy		
Immune system disorders					Anaphylaxis; hypersensitivity
Psychiatric disorders			Insomnia		
Nervous system disorders	Headache			Acute peripheral facial paralysis†	
Gastrointestinal disorders		Nausea			
Musculoskeletal and connective tissue disorders	Arthralgia; myalgia		Pain in extremity		
General disorders and administration site conditions	Injection site pain; fatigue; chills; pyrexia*; injection site swelling	Injection site redness	Malaise; injection site pruritus		

* A higher frequency of pyrexia was observed after the 2nd dose.

† Throughout the safety follow-up period to date, acute peripheral facial paralysis (or palsy) was reported by four participants in the COVID-19 mRNA Vaccine group. Onset was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.

The safety profile in 545 subjects receiving Comirnaty, that were seropositive for SARS-CoV-2 at baseline, was similar to that seen in the general population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V and include batch/Lot number if available.

4.9 Overdose

Overdose data is available from 52 study participants included in the clinical trial that due to an error in dilution received 58 micrograms of Comirnaty. The vaccine recipients did not report an increase in reactogenicity or adverse reactions.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vaccines, other viral vaccines, ATC code: J07BX03

Mechanism of action

The nucleoside-modified messenger RNA in Comirnaty is formulated in lipid nanoparticles, which enable delivery of the non replicating RNA into host cells to direct transient expression of the SARS-CoV-2 S antigen. The mRNA codes for membrane-anchored, full-length S with two point mutations within the central helix. Mutation of these two amino acids to proline locks S in an antigenically preferred prefusion conformation. The vaccine elicits both neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19.

Efficacy

Study 2 is a multicentre, multinational, Phase 1/2/3 randomised, placebo-controlled, observer-blind dose-finding, vaccine candidate selection and efficacy study in participants 12 years of age and older. Randomisation was stratified by age: 12 through 15 years of age, 16 through 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥ 56-year stratum. The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19. Participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrolment, were included as were participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis B virus (HBV). At the time of the analysis of Study 2, information presented is based on participants 16 years and older.

Efficacy in participants 16 years of age and older

In the Phase 2/3 portion, approximately 44,000 participants were randomised equally and were to receive 2 doses of COVID-19 mRNA Vaccine or placebo separated by 21 days. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. Participants are planned to be followed for up to 24 months after Dose 2, for assessments of safety and efficacy against COVID-19. In the clinical study, participants were required to observe a minimum interval of 14 days before and after administration of an influenza vaccine in order to receive either placebo or COVID-19 mRNA Vaccine. In the clinical study, participants were required to observe a minimum interval of 60 days before or after receipt of blood/plasma products or immunoglobulins within through conclusion of the study in order to receive either placebo or COVID-19 mRNA Vaccine.

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. In addition, 134 participants were between the ages of 16 to 17 years of age (66 in the COVID-19 mRNA Vaccine group and 68 in the placebo group) and 1616 participants 75 years of age and older (804 in the COVID-19 mRNA Vaccine group and 812 in the placebo group).

Efficacy against COVID-19

At the time of the primary efficacy analysis, participants had been followed for symptomatic COVID-19 for in total 2,214 person-years for the COVID-19 mRNA Vaccine and in total 2,222 person-years in the placebo group.

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).

The vaccine efficacy information is presented in Table 2.

Table 2: Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants 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*			
Subgroup	**COVID-19 mRNA Vaccine 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)[f]
All subjects[e]	8 2.214 (17,411)	162 2.222 (17,511)	95.0 (90.0, 97.9)
16 to 64 years	7 1.706 (13,549)	143 1.710 (13,618)	95.1 (89.6, 98.1)
65 years and older	1 0.508 (3848)	19 0.511 (3880)	94.7 (66.7, 99.9)
65 to 74 years	1 0.406 (3074)	14 0.406 (3095)	92.9 (53.1, 99.8)
75 years and older	0 0.102 (774)	5 0.106 (785)	100.0 (-13.1, 100.0)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 [*Case definition: (at least 1 of) 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, diarrhoea or vomiting.]

* Participants 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 nucleic acid amplification tests (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 subjects 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 subjects at risk for the endpoint.
e. No confirmed cases were identified in participants 12 to 15 years of age.
f. Confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time. CI not adjusted for multiplicity.

In the second primary analysis, compared to placebo, efficacy of COVID-19 mRNA Vaccine in participants from first COVID-19 occurrence from 7 days after Dose 2 compared to participants with or without evidence of prior infection with SARS-CoV-2 was 94.6% (95% credible interval of 89.9% to 97.3%) in participants 16 years of age and older.

Additionally, subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across genders, ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Comirnaty in the paediatric population in prevention of COVID-19 (see section 4.2 for information on paediatric use).

This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited. The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

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 reproductive and developmental toxicity.

General toxicity

Rats intramuscularly administered Comirnaty (receiving 3 full human doses once weekly, generating relatively higher levels in rats due to body weight differences) demonstrated some injection site oedema and erythema and increases in white blood cells (including basophils and eosinophils) consistent with an inflammatory response as well as vacuolation of portal hepatocytes without evidence of liver injury. All effects were reversible.

Genotoxicity/Carcinogenicity

Neither genotoxicity nor carcinogenicity studies were performed. The components of the vaccine (lipids and mRNA) are not expected to have genotoxic potential.

Reproductive toxicity

Reproductive and developmental toxicity were investigated in rats in a combined fertility and developmental toxicity study where female rats were intramuscularly administered Comirnaty prior to mating and during gestation (receiving 4 full human doses that generate relatively higher levels in rat due to body weight differences, spanning between pre-mating day 21 and gestational day 20). SARS-CoV-2 neutralizing antibody responses were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in foetuses and offspring. There were no vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development. No Comirnaty data are available on vaccine placental transfer or excretion in milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)
2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)
1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
Cholesterol
Potassium chloride
Potassium dihydrogen phosphate
Sodium chloride

Disodium phosphate dihydrate
Sucrose
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial

6 months at -90 °C to -60 °C.

Once removed from the freezer, the unopened vaccine can be stored for up to 5 days at 2 °C to 8 °C, and up to 2 hours at temperatures up to 30 °C, prior to use.

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

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

Diluted medicinal product

Chemical and physical in-use stability 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

Store in a freezer at -90 °C to -60 °C.
Store in the original package in order to protect from light.
During storage, minimise exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.
Thawed vials can be handled in room light conditions.

When you are ready to thaw or use the vaccine

- Open-lid vial trays, or vial trays containing less than 195 vials removed from frozen storage (< -60 °C) may be at room temperature (< 25 °C) for up to 3 minutes to remove vials or for transfer between ultra-low-temperature environments.
- Once a vial is removed from the vial tray, it should be thawed for use.
- After vial trays are returned to frozen storage following room temperature exposure, they must remain in frozen storage for at least 2 hours before they can be removed again.

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

6.5 Nature and contents of container

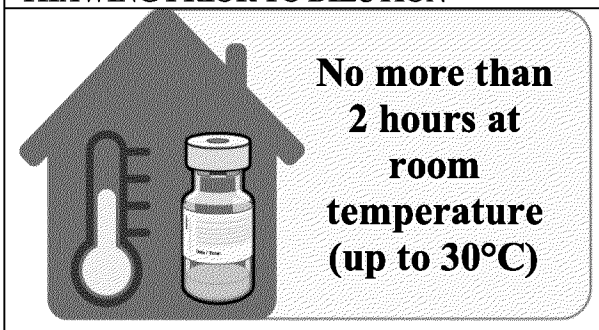
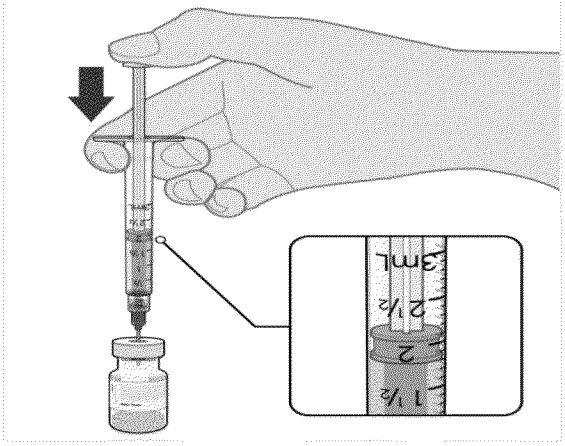
2 mL clear multidose vial (type I glass) with a stopper (synthetic bromobutyl rubber) and a flip-off plastic cap with aluminium seal. Each vial contains 6 doses, see section 6.6.

Pack size: 195 vials

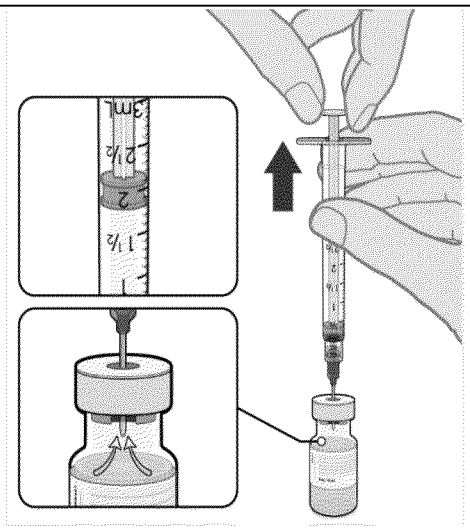
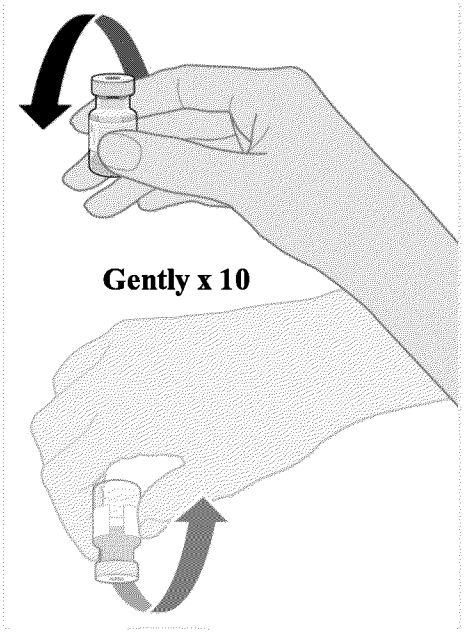
6.6 Special precautions for disposal and other handling

Handling instructions

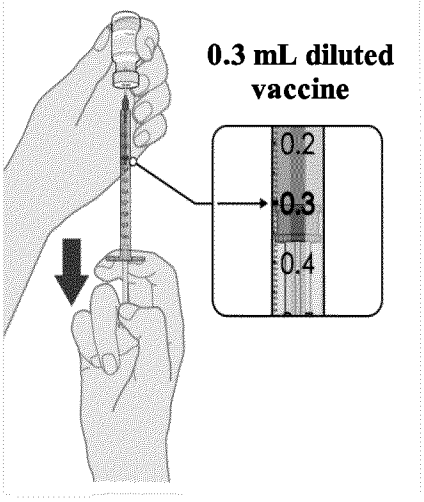
Comirnaty should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

<table>
<tr><th colspan="2">THAWING PRIOR TO DILUTION</th></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.
• 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>
<tr><th colspan="2">DILUTION</th></tr>
<tr><td> 

1.8 mL of 0.9% sodium chloride injection</td><td>• 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.</td></tr>
</table>

 **Pull back plunger to 1.8 mL to remove air from vial**	• Equalise vial pressure before removing the needle from the vial stopper by withdrawing 1.8 mL air into the empty diluent syringe.
 **Gently x 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. Discard the diluted vaccine if particulates or discolouration are present.

<table>
<tr>
<td> 

Record appropriate date and time.
Use within 6 hours after dilution</td>
<td>• The diluted vials should be marked with the appropriate date and time.
• Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.</td>
</tr>
<tr>
<td colspan="2">PREPARATION OF INDIVIDUAL 0.3 mL DOSES OF COMIRNATY</td>
</tr>
<tr>
<td> 
</td>
<td>• 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 Comirnaty.

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

If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial.
• Each dose 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.</td>
</tr>
</table>

Disposal

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

7. MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz
Germany
Phone: +49 6131 90840
Fax: +49 6131 9084390
info@biontech.de

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1528

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 December 2020

10. DATE OF REVISION OF THE TEXT

{DD Month YYYY}

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCES AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCES AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance(s)

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz
Germany

Rentschler Biopharma SE
Erwin-Rentschler-Strasse 21
88471 Laupheim
Germany

Wyeth BioPharma Division of Wyeth Pharmaceuticals LLC
1 Burtt Road
Andover, MA 01810
USA

Name and address of the manufacturers responsible for batch release

BioNTech Manufacturing GmbH
Kupferbergterrasse 17 - 19
55116 Mainz
Germany

Pfizer Manufacturing Belgium NV
Rijksweg 12
2870 Puurs
Belgium

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

In view of the declared Public Health Emergency of International Concern and in order to ensure early supply this medicinal product is subject to a time-limited exemption allowing reliance on batch control testing conducted in the registered site(s) that are located in a third country. This exemption ceases to be valid on 31 August 2021. Implementation of EU based batch control arrangements, including the necessary variations to the terms of the marketing authorisation, has to be completed by 31 August 2021 at the latest, in line with the agreed plan for this transfer of testing. Progress reports have to be submitted on 31 March 2021 and included in the annual renewal application.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

- **Official batch release**

In accordance with Article 114 of Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to complete the characterisation of the active substance and finished product, the MAH should provide additional data.	July 2021. Interim reports: 31 March 2021
In order to ensure consistent product quality, the MAH should provide additional information to enhance the control strategy, including the active substance and finished product specifications.	July 2021. Interim reports: March 2021
In order to confirm the consistency of the finished product manufacturing process, the MAH should provide additional validation data.	March 2021
In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional information about the synthetic process and control strategy for the excipient ALC-0315.	July 2021. Interim reports: January 2021, April 2021
In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional information about the synthetic process and control strategy for the excipient ALC-0159.	July 2021. Interim reports: January 2021, April 2021

Description	Due date
In order to confirm the efficacy and safety of Comirnaty, the MAH should submit the final Clinical Study Report for the randomized, placebo-controlled, observer-blind study C4591001.	December 2023

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON BOX LABEL

1. NAME OF THE MEDICINAL PRODUCT

COMIRNATY concentrate for dispersion for injection
COVID-19 mRNA Vaccine (nucleoside modified)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After dilution each vial contains 6 doses of 0.3 mL.

3. LIST OF EXCIPIENTS

Excipients: ALC-0315, ALC-0159, DSPC, cholesterol, potassium chloride, potassium dihydrogen phosphate, sodium chloride, disodium phosphate dihydrate, sucrose, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for dispersion for injection
195 multidose vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use after dilution.
Read the package leaflet before use.

Scan QR code for more information.

Dilute before use: Dilute each vial with 1.8 mL sodium chloride 9 mg/mL (0.9%) solution for injection.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Storage:
Prior to dilution, store at -90 °C to -60 °C in the original package in order to protect from light.
After dilution, store the vaccine at 2 °C to 30 °C and use within 6 hours. Discard any unused vaccine.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1528

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

COMIRNATY sterile concentrate
COVID-19 mRNA Vaccine
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6 doses after dilution

6. OTHER

Discard date/time:

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Comirnaty concentrate for dispersion for injection
COVID-19 mRNA Vaccine (nucleoside modified)

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you receive this vaccine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Comirnaty is and what it is used for

Comirnaty is a vaccine used for preventing COVID-19 caused by SARS-CoV-2 virus.

Comirnaty is given to adults and adolescents from 16 years of age and older.

The vaccine causes the immune system (the body's natural defences) to produce antibodies and blood cells that work against the virus, so giving protection against COVID-19.

As Comirnaty does not contain the virus to produce immunity, it cannot give you COVID-19.

2. What you need to know before you receive Comirnaty

Comirnaty should not be given
- if you are allergic to the active substance or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions
Talk to your doctor, pharmacist or nurse before you are given the vaccine if:
- you have ever had a severe allergic reaction or breathing problems after any other vaccine injection or after you were given Comirnaty in the past.
- you have ever fainted following any needle injection.
- you have a severe illness or infection with high fever. However, you can have your vaccination if you have a mild fever or upper airway infection like a cold.
- you have a bleeding problem, you bruise easily or you use a medicine to prevent blood-clots.
- you have a weakened immune system, because of a disease such as HIV infection or a medicine such as corticosteroid that affects your immune system

As with any vaccine, the 2-dose vaccination course of Comirnaty may not fully protect all those who receive it and it is not known how long you will be protected.

Children and adolescents
Comirnaty is not recommended for children aged under 16 years.

Other medicines and Comirnaty
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines or have recently received any other vaccine.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before you receive this vaccine.

Driving and using machines
Some of the effects of vaccination mentioned in section 4 (Possible side effects) may temporarily affect your ability to drive or use machines. Wait until these effects have worn off before you drive or use machines.

Comirnaty contains potassium and sodium
This vaccine contains less than 1 mmol potassium (39 mg) per dose, that is to say essentially 'potassium-free'.

This vaccine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

3. How Comirnaty is given

Comirnaty is given after dilution as an injection of 0.3 mL into a muscle of your upper arm.

You will receive 2 injections, given at least 21 days apart.

After the first dose of Comirnaty, you should receive a second dose of the same vaccine after 21 days to complete the vaccination course.

If you have any further questions on the use of Comirnaty, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all vaccines, Comirnaty can cause side effects, although not everybody gets them.

Very common side effects: may affect more than 1 in 10 people
- injection site: pain, swelling
- tiredness
- headache
- muscle pain
- joint pain
- chills, fever

Common side effects: may affect up to 1 in 10 people
- injection site redness
- nausea

Uncommon side effects: may affect up to 1 in 100 people
- enlarged lymph nodes
- feeling unwell
- pain in limb
- insomnia
- injection site itching

Rare side effects: may affect up to 1 in 1,000 people
- temporary one sided facial drooping

Not known (cannot be estimated from the available data)
- severe allergic reaction

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V and include batch/Lot number if available. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Comirnaty

Keep this medicine out of the sight and reach of children.

The following information about storage, expiry and use and handling is intended for healthcare professionals.

Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.

Store in freezer at -90 °C to -60 °C.

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

After thawing, the vaccine should be diluted and used immediately. However, in-use stability data have demonstrated that once removed from freezer, the undiluted vaccine can be stored for up to 5 days at 2 °C to 8 °C, or up to 2 hours at temperatures up to 30 °C, prior to use.

After dilution, store the vaccine at 2 °C to 30 °C and use within 6 hours. Discard any unused vaccine.

Once removed from the freezer and diluted, the vials should be marked with the new discard date and time. Once thawed, the vaccine cannot be re-frozen.

Do not use this vaccine if you notice particulates in the dilution or discolouration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Comirnaty contains

- The active substance is COVID-19 mRNA Vaccine. After dilution, the vial contains 6 doses of 0.3 mL with 30 micrograms mRNA each.
- The other ingredients are:
  - ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)
  - 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)
  - 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
  - cholesterol
  - potassium chloride
  - potassium dihydrogen phosphate
  - sodium chloride
  - disodium phosphate dihydrate
  - sucrose
  - water for injections

What Comirnaty looks like and contents of the pack

The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9) provided in a multidose vial of 6 doses in a 2 mL clear vial (type I glass), with a rubber stopper and a flip-off plastic cap with aluminium seal.

Pack size: 195 vials

Marketing Authorisation Holder

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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in {MM/YYYY}

This medicine has been given 'conditional approval'. This means that there is more evidence to come about this medicine. The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Scan the code with a mobile device to get the package leaflet in different languages.

URL: www.comirnatyglobal.com

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

This package leaflet is available in all EU/EEA languages on the European Medicines Agency website.

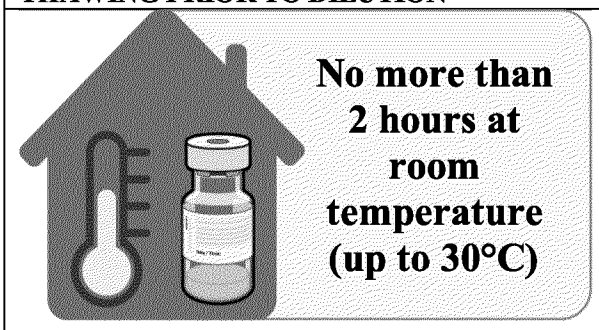
The following information is intended for healthcare professionals only:

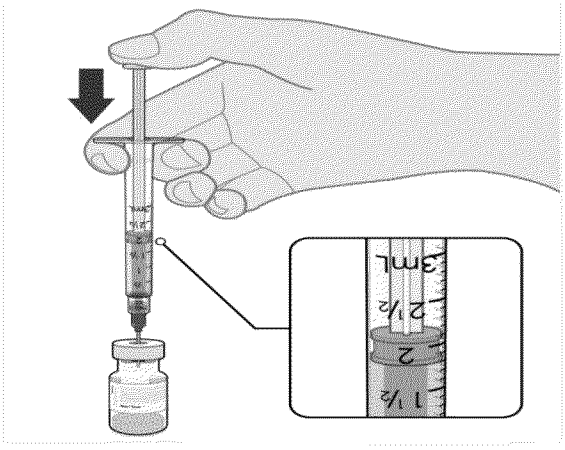
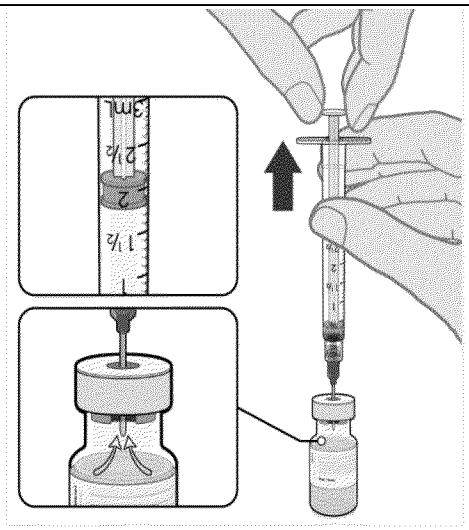
Administer Comirnaty intramuscularly after dilution as a course of 2 doses (0.3 mL each) at least 21 days apart.

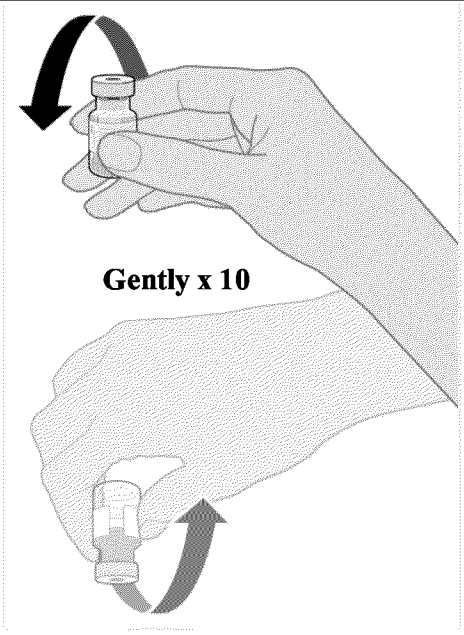
Traceability

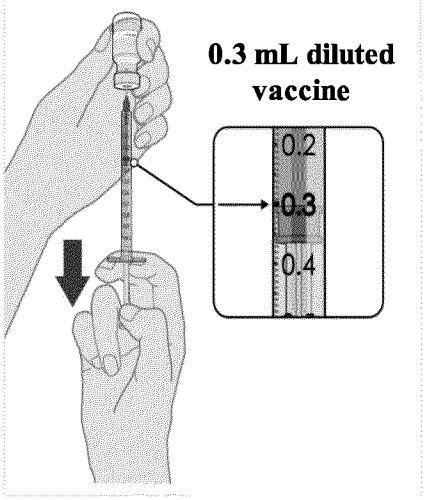
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Handling instructions
Comirnaty 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. • 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**	• Equalise 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. Discard the diluted vaccine if particulates or discolouration 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. • 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 Comirnaty. Low dead-volume syringes and/or needles should be used in order to extract 6 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial. • Each dose 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.

ANNEX IV

CONCLUSIONS ON THE GRANTING OF THE CONDITIONAL MARKETING AUTHORISATION PRESENTED BY THE EUROPEAN MEDICINES AGENCY

Conclusions presented by the European Medicines Agency on:

- **Conditional marketing authorisation**

The CHMP having considered the application is of the opinion that the risk-benefit balance is favourable to recommend the granting of the conditional marketing authorisation as further explained in the European Public Assessment Report.

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Comirnaty concentrate for dispersion for injection
COVID-19 mRNA Vaccine (nucleoside modified)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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.

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

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 SARS-CoV-2.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for dispersion for injection (sterile concentrate).
The vaccine is a white to off-white frozen dispersion (pH: 6.9 - 7.9).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Comirnaty is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 16 years of age and older.

The use of this vaccine should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Individuals 16 years of age and older
Comirnaty is administered intramuscularly after dilution as a course of 2 doses (0.3 mL each). It is recommended to administer the second dose 3 weeks after the first dose (see sections 4.4 and 5.1).

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

Paediatric population
The safety and efficacy of Comirnaty in children and adolescents aged less than 16 years of age have not yet been established. Limited data are available.

Elderly population
No dosage adjustment is required in elderly individuals ≥ 65 years of age.

Method of administration

Comirnaty should be administered intramuscularly after dilution (see section 6.6).

After dilution, vials of Comirnaty contain six doses of 0.3 mL of vaccine. In order to extract six doses from a single vial, low dead-volume syringes and/or needles should be used. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial. 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.

The preferred site is the deltoid muscle of the upper arm.

Do not inject the vaccine intravascularly, subcutaneously or intradermally.

The vaccine should not be mixed in the same syringe with any other vaccines or medicinal products.

For precautions to be taken before administering the vaccine, see section 4.4.

For instructions regarding thawing, handling and disposal of the vaccine, 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

Hypersensitivity and anaphylaxis
Events of anaphylaxis have been reported. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine.

Close observation for at least 15 minutes is recommended following vaccination. A second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose of Comirnaty.

Anxiety-related reactions
Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions may occur in association with vaccination as a psychogenic response to the needle injection. It is important that precautions are in place to avoid injury from fainting.

Concurrent illness
Vaccination should be postponed in individuals suffering from acute severe febrile illness or acute infection. The presence of a minor infection and/or low-grade fever should not delay vaccination.

Thrombocytopenia and coagulation disorders
As with other intramuscular injections, the vaccine should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia) because bleeding or bruising may occur following an intramuscular administration in these individuals.

Immunocompromised individuals
The efficacy, safety and immunogenicity of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of Comirnaty may be lower in immunosuppressed individuals.

Duration of protection
The duration of protection afforded by the vaccine is unknown as it is still being determined by ongoing clinical trials.

Limitations of vaccine effectiveness
As with any vaccine, vaccination with Comirnaty may not protect all vaccine recipients. Individuals may not be fully protected until 7 days after their second dose of vaccine.

Excipients

This vaccine contains less than 1 mmol potassium (39 mg) per dose, that is to say essentially 'potassium-free'.

This vaccine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concomitant administration of Comirnaty with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is limited experience with use of Comirnaty in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development (see section 5.3). Administration of Comirnaty in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and foetus.

Breast-feeding

It is unknown whether Comirnaty is excreted in human milk.

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of safety profile

The safety of Comirnaty was evaluated in participants 16 years of age and older in 2 clinical studies that included 21,744 participants that have received at least one dose of Comirnaty.

In Study 2, a total of 21,720 participants 16 years of age or older received at least 1 dose of Comirnaty and a total of 21,728 participants 16 years of age or older received placebo (including 138 and 145 adolescents 16 and 17 years of age in the vaccine and placebo groups, respectively). A total of 20,519 participants 16 years of age or older received 2 doses of Comirnaty.

At the time of the analysis of Study 2, a total of 19,067 (9,531 Comirnaty and 9,536 placebo) participants 16 years of age or older were evaluated for safety for at least 2 months after the second dose of Comirnaty. This included a total of 10,727 (5,350 Comirnaty and 5,377 placebo) participants 16 to 55 years of age and a total of 8,340 (4,181 Comirnaty and 4,159 placebo) participants 56 years and older.

The most frequent adverse reactions in participants 16 years of age and older were injection site pain (> 80%), fatigue (> 60%), headache (> 50%), myalgia and 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. A slightly lower frequency of reactogenicity events was associated with greater age.

Tabulated list of adverse reactions from clinical studies

Adverse reactions observed during clinical studies are listed below according to the following frequency categories:

Very common (≥ 1/10),
Common (≥ 1/100 to < 1/10),
Uncommon (≥ 1/1,000 to < 1/100),
Rare (≥ 1/10,000 to < 1/1,000),
Very rare (< 1/10,000),
Not known (cannot be estimated from the available data).

Table 1: Adverse reactions from Comirnaty clinical trials

System Organ Class	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)	Not known (cannot be estimated from the available data)
Blood and lymphatic system disorders			Lymphadenopathy		
Immune system disorders					Anaphylaxis; hypersensitivity
Psychiatric disorders			Insomnia		

System Organ Class	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)	Not known (cannot be estimated from the available data)
Nervous system disorders	Headache			Acute peripheral facial paralysis†	
Gastrointestinal disorders		Nausea			
Musculoskeletal and connective tissue disorders	Arthralgia; myalgia		Pain in extremity		
General disorders and administration site conditions	Injection site pain; fatigue; chills; pyrexia*; injection site swelling	Injection site redness	Malaise; injection site pruritus		

* A higher frequency of pyrexia was observed after the 2nd dose.

† Throughout the safety follow-up period to date, acute peripheral facial paralysis (or palsy) was reported by four participants in the COVID-19 mRNA Vaccine group. Onset was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.

The safety profile in 545 subjects receiving Comirnaty, that were seropositive for SARS-CoV-2 at baseline, was similar to that seen in the general population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V and include batch/Lot number if available.

4.9 Overdose

Overdose data is available from 52 study participants included in the clinical trial that due to an error in dilution received 58 micrograms of Comirnaty. The vaccine recipients did not report an increase in reactogenicity or adverse reactions.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vaccines, other viral vaccines, ATC code: J07BX03

Mechanism of action

The nucleoside-modified messenger RNA in Comirnaty is formulated in lipid nanoparticles, which enable delivery of the non replicating RNA into host cells to direct transient expression of the SARS-CoV-2 S antigen. The mRNA codes for membrane-anchored, full-length S with two point mutations within the central helix. Mutation of these two amino acids to proline locks S in an antigenically preferred prefusion conformation. The vaccine elicits both neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19.

Efficacy

Study 2 is a multicentre, multinational, Phase 1/2/3 randomised, placebo-controlled, observer-blind dose-finding, vaccine candidate selection and efficacy study in participants 12 years of age and older. Randomisation was stratified by age: 12 through 15 years of age, 16 through 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥ 56-year stratum. The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19. Participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrolment, were included as were participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis B virus (HBV). At the time of the analysis of Study 2, information presented is based on participants 16 years and older.

Efficacy in participants 16 years of age and older

In the Phase 2/3 portion, approximately 44,000 participants were randomised equally and were to receive 2 doses of COVID-19 mRNA Vaccine or placebo separated by 21 days. 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. Participants are planned to be followed for up to 24 months after Dose 2, for assessments of safety and efficacy against COVID-19. In the clinical study, participants were required to observe a minimum interval of 14 days before and after administration of an influenza vaccine in order to receive either placebo or COVID-19 mRNA Vaccine. In the clinical study, participants were required to observe a minimum interval of 60 days before or after receipt of blood/plasma products or immunoglobulins within through conclusion of the study in order to receive either placebo or COVID-19 mRNA Vaccine.

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. In addition, 134 participants were between the ages of 16 to 17 years of age (66 in the COVID-19 mRNA Vaccine group and 68 in the placebo group) and 1,616 participants 75 years of age and older (804 in the COVID-19 mRNA Vaccine group and 812 in the placebo group).

Efficacy against COVID-19

At the time of the primary efficacy analysis, participants had been followed for symptomatic COVID-19 for in total 2,214 person-years for the COVID-19 mRNA Vaccine and in total 2,222 person-years in the placebo group.

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).

The vaccine efficacy information is presented in Table 2.

Table 2: Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants 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*			
Subgroup	**COVID-19 mRNA Vaccine 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)[f]
All subjects[e]	8 2.214 (17,411)	162 2.222 (17,511)	95.0 (90.0, 97.9)
16 to 64 years	7 1.706 (13,549)	143 1.710 (13,618)	95.1 (89.6, 98.1)
65 years and older	1 0.508 (3848)	19 0.511 (3880)	94.7 (66.7, 99.9)
65 to 74 years	1 0.406 (3074)	14 0.406 (3095)	92.9 (53.1, 99.8)
75 years and older	0 0.102 (774)	5 0.106 (785)	100.0 (-13.1, 100.0)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 [*Case definition: (at least 1 of) 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, diarrhoea or vomiting.]

* Participants 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 nucleic acid amplification tests (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 subjects 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 subjects at risk for the endpoint.
e. No confirmed cases were identified in participants 12 to 15 years of age.
f. Confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time. CI not adjusted for multiplicity.

In the second primary analysis, compared to placebo, efficacy of COVID-19 mRNA Vaccine in participants from first COVID-19 occurrence from 7 days after Dose 2 compared to participants with or without evidence of prior infection with SARS-CoV-2 was 94.6% (95% credible interval of 89.9% to 97.3%) in participants 16 years of age and older.

Additionally, subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across genders, ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Comirnaty in the paediatric population in prevention of COVID-19 (see section 4.2 for information on paediatric use).

This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited. The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

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 reproductive and developmental toxicity.

General toxicity

Rats intramuscularly administered Comirnaty (receiving 3 full human doses once weekly, generating relatively higher levels in rats due to body weight differences) demonstrated some injection site oedema and erythema and increases in white blood cells (including basophils and eosinophils) consistent with an inflammatory response as well as vacuolation of portal hepatocytes without evidence of liver injury. All effects were reversible.

Genotoxicity/Carcinogenicity

Neither genotoxicity nor carcinogenicity studies were performed. The components of the vaccine (lipids and mRNA) are not expected to have genotoxic potential.

Reproductive toxicity

Reproductive and developmental toxicity were investigated in rats in a combined fertility and developmental toxicity study where female rats were intramuscularly administered Comirnaty prior to mating and during gestation (receiving 4 full human doses that generate relatively higher levels in rat due to body weight differences, spanning between pre-mating day 21 and gestational day 20). SARS-CoV-2 neutralizing antibody responses were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in foetuses and offspring. There were no vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development. No Comirnaty data are available on vaccine placental transfer or excretion in milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)
2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)
1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
Cholesterol
Potassium chloride
Potassium dihydrogen phosphate
Sodium chloride

Disodium phosphate dihydrate
Sucrose
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial

6 months at -90 °C to -60 °C.

Once removed from the freezer, the unopened vaccine can be stored for up to 5 days at 2 °C to 8 °C, and up to 2 hours at temperatures up to 30 °C, prior to use.

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

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

Diluted medicinal product

Chemical and physical in-use stability 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

Store in a freezer at -90 °C to -60 °C.
Store in the original package in order to protect from light.
During storage, minimise exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.
Thawed vials can be handled in room light conditions.

When you are ready to thaw or use the vaccine

- Open-lid vial trays, or vial trays containing less than 195 vials removed from frozen storage (< -60 °C) may be at room temperature (< 25 °C) for up to 3 minutes to remove vials or for transfer between ultra-low-temperature environments.
- Once a vial is removed from the vial tray, it should be thawed for use.
- After vial trays are returned to frozen storage following room temperature exposure, they must remain in frozen storage for at least 2 hours before they can be removed again.

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

6.5 Nature and contents of container

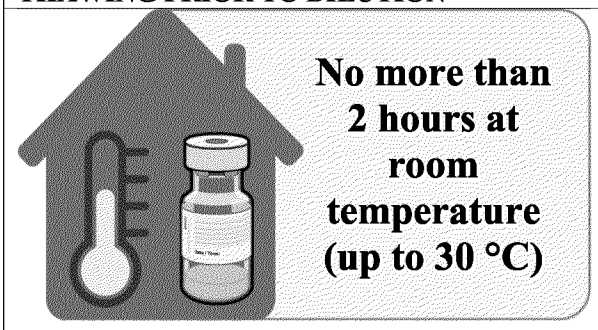
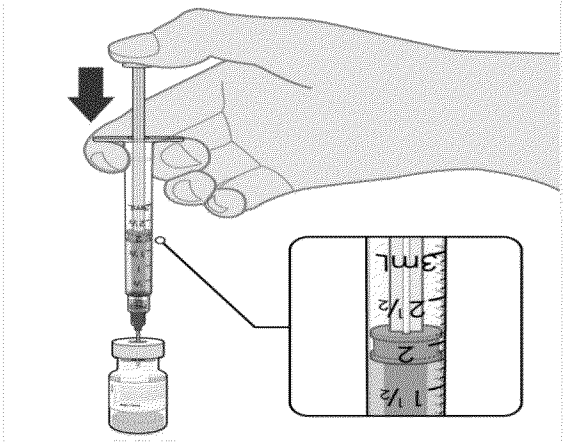
2 mL clear multidose vial (type I glass) with a stopper (synthetic bromobutyl rubber) and a flip-off plastic cap with aluminium seal. Each vial contains 6 doses, see section 6.6.

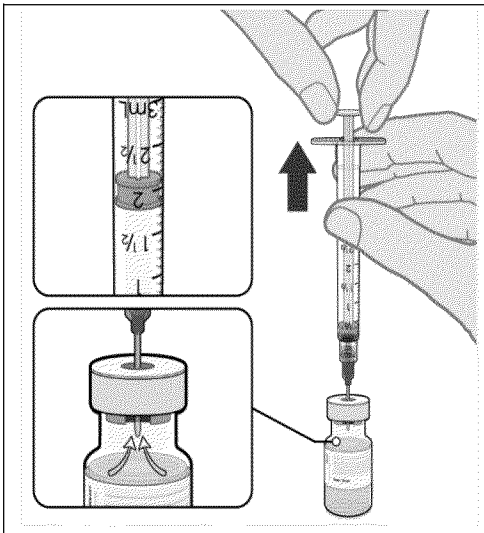
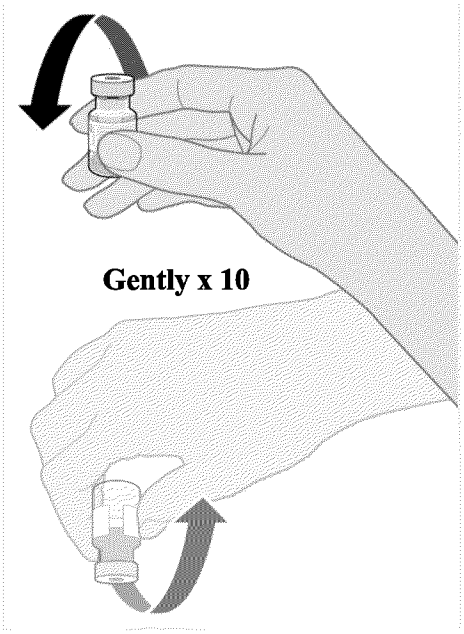
Pack size: 195 vials

6.6 Special precautions for disposal and other handling

Handling instructions

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

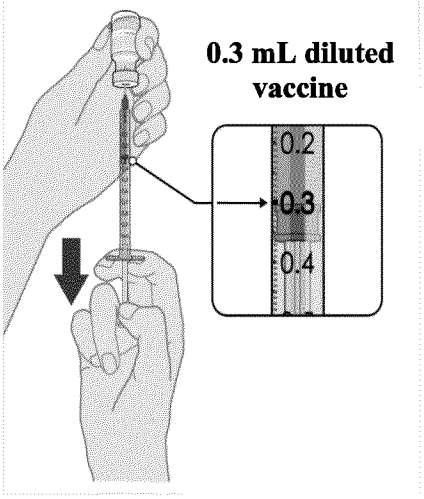
THAWING PRIOR TO DILUTION	
	• The multidose vial is stored frozen and must be thawed prior to dilution. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 195 vial pack may take 3 hours to thaw. Alternatively, frozen vials may also be thawed for 30 minutes at temperatures up to 30 °C for immediate use. • 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**	• Equalise vial pressure before removing the needle from the vial stopper by withdrawing 1.8 mL air into the empty diluent syringe.
 **Gently x 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. Discard the diluted vaccine if particulates or discolouration 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.
- 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 Comirnaty.

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

  If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial.
- Each dose 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. MARKETING AUTHORISATION HOLDER

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Fax: +49 6131 9084390
info@biontech.de

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1528

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 December 2020

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCES AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCES AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance(s)

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz
Germany

Rentschler Biopharma SE
Erwin-Rentschler-Strasse 21
88471 Laupheim
Germany

Wyeth BioPharma Division of Wyeth Pharmaceuticals LLC
1 Burtt Road
Andover, MA 01810
USA

Name and address of the manufacturers responsible for batch release

BioNTech Manufacturing GmbH
Kupferbergterrasse 17 - 19
55116 Mainz
Germany

Pfizer Manufacturing Belgium NV
Rijksweg 12
2870 Puurs
Belgium

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

In view of the declared Public Health Emergency of International Concern and in order to ensure early supply this medicinal product is subject to a time-limited exemption allowing reliance on batch control testing conducted in the registered site(s) that are located in a third country. This exemption ceases to be valid on 31 August 2021. Implementation of EU based batch control arrangements, including the necessary variations to the terms of the marketing authorisation, has to be completed by 31 August 2021 at the latest, in line with the agreed plan for this transfer of testing. Progress reports have to be submitted on 31 March 2021 and included in the annual renewal application.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

- **Official batch release**

In accordance with Article 114 of Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to complete the characterisation of the active substance and finished product, the MAH should provide additional data.	July 2021. Interim reports: 31 March 2021
In order to ensure consistent product quality, the MAH should provide additional information to enhance the control strategy, including the active substance and finished product specifications.	July 2021. Interim reports: March 2021
In order to confirm the consistency of the finished product manufacturing process, the MAH should provide additional validation data.	March 2021
In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional information about the synthetic process and control strategy for the excipient ALC-0315.	July 2021. Interim reports: January 2021, April 2021
In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional information about the synthetic process and control strategy for the excipient ALC-0159.	July 2021. Interim reports: January 2021, April 2021

Description	Due date
In order to confirm the efficacy and safety of Comirnaty, the MAH should submit the final Clinical Study Report for the randomized, placebo-controlled, observer-blind study C4591001.	December 2023

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON BOX LABEL

1. NAME OF THE MEDICINAL PRODUCT

COMIRNATY concentrate for dispersion for injection
COVID-19 mRNA Vaccine (nucleoside modified)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After dilution each vial contains 6 doses of 0.3 mL.

3. LIST OF EXCIPIENTS

Excipients: ALC-0315, ALC-0159, DSPC, cholesterol, potassium chloride, potassium dihydrogen phosphate, sodium chloride, disodium phosphate dihydrate, sucrose, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for dispersion for injection
195 multidose vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use after dilution.
Read the package leaflet before use.

Scan QR code for more information.

Dilute before use: Dilute each vial with 1.8 mL sodium chloride 9 mg/mL (0.9%) solution for injection.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Storage:
Prior to dilution, store at -90 °C to -60 °C in the original package in order to protect from light.
After dilution, store the vaccine at 2 °C to 30 °C and use within 6 hours. Discard any unused vaccine.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1528

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

COMIRNATY sterile concentrate
COVID-19 mRNA Vaccine
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6 doses after dilution

6. OTHER

Discard date/time:

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Comirnaty concentrate for dispersion for injection
COVID-19 mRNA Vaccine (nucleoside modified)

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you receive this vaccine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Comirnaty is and what it is used for

Comirnaty is a vaccine used for preventing COVID-19 caused by SARS-CoV-2 virus.

Comirnaty is given to adults and adolescents from 16 years of age and older.

The vaccine causes the immune system (the body's natural defences) to produce antibodies and blood cells that work against the virus, so giving protection against COVID-19.

As Comirnaty does not contain the virus to produce immunity, it cannot give you COVID-19.

2. What you need to know before you receive Comirnaty

Comirnaty should not be given
- if you are allergic to the active substance or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions
Talk to your doctor, pharmacist or nurse before you are given the vaccine if:
- you have ever had a severe allergic reaction or breathing problems after any other vaccine injection or after you were given Comirnaty in the past.
- you have ever fainted following any needle injection.
- you have a severe illness or infection with high fever. However, you can have your vaccination if you have a mild fever or upper airway infection like a cold.
- you have a bleeding problem, you bruise easily or you use a medicine to prevent blood-clots.
- you have a weakened immune system, because of a disease such as HIV infection or a medicine such as corticosteroid that affects your immune system

As with any vaccine, the 2-dose vaccination course of Comirnaty may not fully protect all those who receive it and it is not known how long you will be protected.

Children and adolescents
Comirnaty is not recommended for children aged under 16 years.

Other medicines and Comirnaty
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines or have recently received any other vaccine.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before you receive this vaccine.

Driving and using machines
Some of the effects of vaccination mentioned in section 4 (Possible side effects) may temporarily affect your ability to drive or use machines. Wait until these effects have worn off before you drive or use machines.

Comirnaty contains potassium and sodium
This vaccine contains less than 1 mmol potassium (39 mg) per dose, that is to say essentially 'potassium-free'.

This vaccine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

3. How Comirnaty is given

Comirnaty is given after dilution as an injection of 0.3 mL into a muscle of your upper arm.

You will receive 2 injections.

It is recommended to receive the second dose of the same vaccine 3 weeks after the first dose to complete the vaccination course.

If you have any further questions on the use of Comirnaty, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all vaccines, Comirnaty can cause side effects, although not everybody gets them.

Very common side effects: may affect more than 1 in 10 people
- injection site: pain, swelling
- tiredness
- headache
- muscle pain
- joint pain
- chills, fever

Common side effects: may affect up to 1 in 10 people
- injection site redness
- nausea

Uncommon side effects: may affect up to 1 in 100 people
- enlarged lymph nodes
- feeling unwell
- pain in limb
- insomnia
- injection site itching

Rare side effects: may affect up to 1 in 1,000 people
- temporary one sided facial drooping

Not known (cannot be estimated from the available data)
- severe allergic reaction

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V and include batch/Lot number if available. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Comirnaty

Keep this medicine out of the sight and reach of children.

The following information about storage, expiry and use and handling is intended for healthcare professionals.

Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.

Store in freezer at -90 °C to -60 °C.

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

After thawing, the vaccine should be diluted and used immediately. However, in-use stability data have demonstrated that once removed from freezer, the undiluted vaccine can be stored for up to 5 days at 2 °C to 8 °C, or up to 2 hours at temperatures up to 30 °C, prior to use.

After dilution, store the vaccine at 2 °C to 30 °C and use within 6 hours. Discard any unused vaccine.

Once removed from the freezer and diluted, the vials should be marked with the new discard date and time. Once thawed, the vaccine cannot be re-frozen.

Do not use this vaccine if you notice particulates in the dilution or discolouration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Comirnaty contains

- The active substance is COVID-19 mRNA Vaccine. After dilution, the vial contains 6 doses of 0.3 mL with 30 micrograms mRNA each.
- The other ingredients are:
  - ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)
  - 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)
  - 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
  - cholesterol
  - potassium chloride
  - potassium dihydrogen phosphate
  - sodium chloride
  - disodium phosphate dihydrate
  - sucrose
  - water for injections

What Comirnaty looks like and contents of the pack

The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9) provided in a multidose vial of 6 doses in a 2 mL clear vial (type I glass), with a rubber stopper and a flip-off plastic cap with aluminium seal.

Pack size: 195 vials

Marketing Authorisation Holder

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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in {MM/YYYY}

This medicine has been given 'conditional approval'. This means that there is more evidence to come about this medicine. The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Scan the code with a mobile device to get the package leaflet in different languages.

URL: www.comirnatyglobal.com

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

This package leaflet is available in all EU/EEA languages on the European Medicines Agency website.

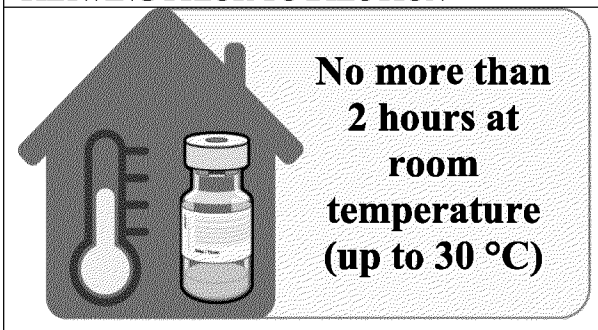
The following information is intended for healthcare professionals only:

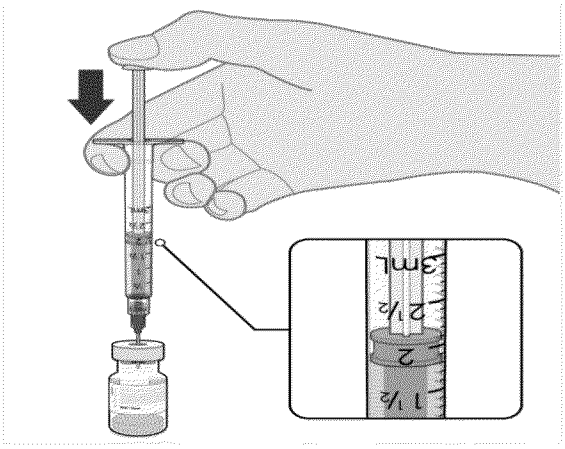
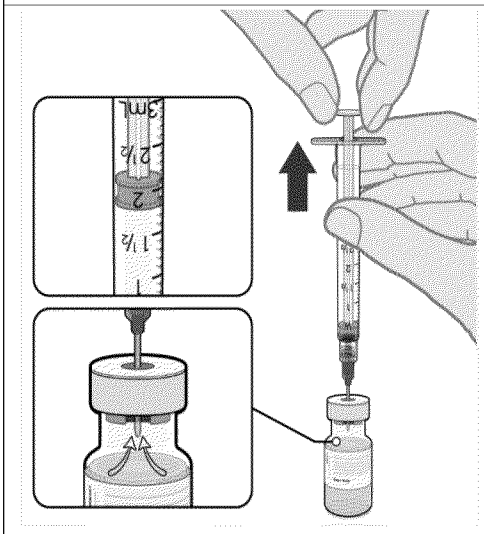
Administer Comirnaty intramuscularly after dilution as a course of 2 doses (0.3 mL each) 3 weeks apart.

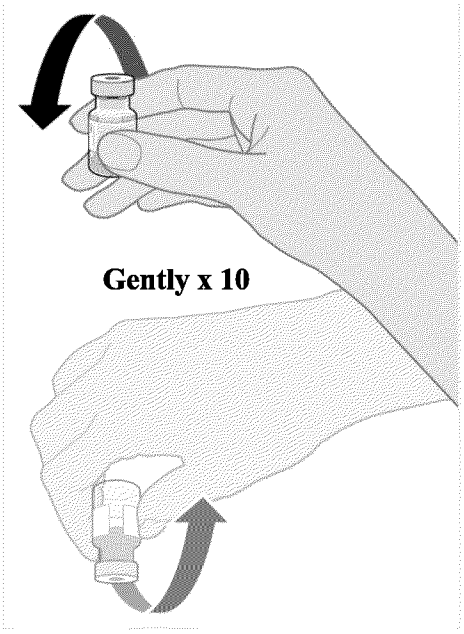
Traceability

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

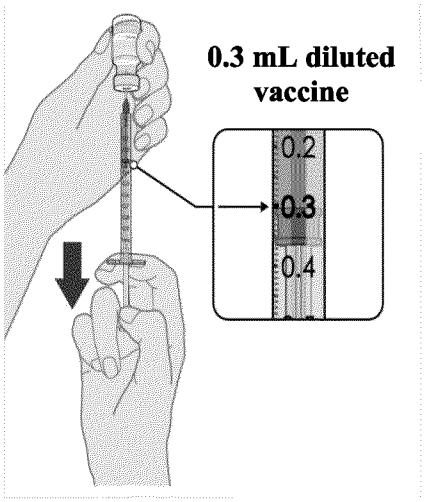
Handling instructions
Comirnaty should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

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. • 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**	• Equalise 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. Discard the diluted vaccine if particulates or discolouration 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. • 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 Comirnaty.

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

  If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial.
- Each dose 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.

APPENDIX 2.1 - Cumulative Summary Tabulation of Serious Adverse Events from Clinical Trials

BNT162B2

Reporting Period: Through 18-JUN-2021
Total Number of Cases: 1,030
Total Number of Adverse Events (PT): 1,285
MedDRA Version: v.24.0J

SOC	PT	BNT162B2;BNT162B2S01	BLINDED THERAPY	PLACEBO	PRE RANDOMIZATION / NO STUDY DRUG
Blood and lymphatic system disorders	Anaemia	1	1		
	Anaemia macrocytic	1			
	Blood loss anaemia	1			
	Febrile neutropenia	1			
	Lymphadenitis		1		
	Lymphadenopathy	1			
	Microcytic anaemia		1		
	Neutropenia		1		
	Pancytopenia	1			
	Red blood cell abnormality		1		
	Thrombocytopenia		2		
Sub Total:		**6**	**7**		
Cardiac disorders	Accelerated idioventricular rhythm	1			
	Acute coronary syndrome	2	5		
	Acute left ventricular failure		1		
	Acute myocardial infarction	4	16		

* 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;BNT162 B2S01	BLINDED THERAPY	PLACEBO	PRE RANDOMIZATION / NO STUDY DRUG
	Angina pectoris	1	2		
	Angina unstable	1	3		
	Aortic valve incompetence			2	
	Arrhythmia supraventricular		1		
	Arteriosclerosis coronary artery		1		
	Arteriospasm coronary	1	1		
	Atrial fibrillation	6	18	1	
	Atrial flutter	2			
	Atrioventricular block complete		1		
	Bradycardia		2		
	Cardiac arrest	1	8		
	Cardiac failure acute			1	
	Cardiac failure chronic			1	
	Cardiac failure congestive	1	6		
	Cardio-respiratory arrest	1	3		
	Cardiovascular disorder	1			
	Conduction disorder	1			
	Coronary artery disease	1	6	2	
	Coronary artery dissection		1		
	Coronary artery occlusion		4		

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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;BNT162 B2S01	BLINDED THERAPY	PLACEBO	PRE RANDOMIZATION / NO STUDY DRUG
	Hypertensive heart disease		1		
	Ischaemic cardiomyopathy	1	1		
	Junctional ectopic tachycardia		1		
	Myocardial infarction	6	11	1	
	Myocardial ischaemia	1	1		
	Nonreassuring foetal heart rate pattern		1		
	Palpitations	1			
	Pericarditis	2			
	Sinus node dysfunction	1			
	Supraventricular extrasystoles	1			
	Supraventricular tachycardia	3			
	Tachyarrhythmia		1		
	Tachycardia		1		
	Ventricular arrhythmia	1			
	Ventricular extrasystoles	1			
	Ventricular fibrillation		1		
	Ventricular tachycardia	2	1		
Sub Total:		**44**	**99**	**8**	
Congenital, familial and genetic disorders	BRCA1 gene mutation	1			
	Congenital bladder neck obstruction			1	

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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.
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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	PRE RANDOMIZATION / NO STUDY DRUG
	Congenital ureteropelvic junction obstruction			1	
	Heart disease congenital		1		
	Hypertrophic cardiomyopathy	1			
	Newborn persistent pulmonary hypertension		1		
	Sickle cell disease		1		
Sub Total:		**2**	**3**	**2**	
Ear and labyrinth disorders	Vertigo	2	3		
Sub Total:		**2**	**3**		
Endocrine disorders	Goitre	1			
Sub Total:		**1**			
Eye disorders	Blindness unilateral		1		
	Choroidal neovascularisation		1		
	Diplopia	2	1		
	Eye haemorrhage			1	
	Optic ischaemic neuropathy	1			
	Retinal artery occlusion		1		
	Retinal detachment	1			
	Retinal tear	1			
	Retinal vein thrombosis		1		
	Visual impairment		2		
Sub Total:		**5**	**7**	**1**	

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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.
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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.
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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;BNT162 B2S01	BLINDED THERAPY	PLACEBO	PRE RANDOMIZATION / NO STUDY DRUG
Gastrointestinal disorders	Abdominal adhesions		1		
	Abdominal hernia		1		
	Abdominal pain		2		
	Abdominal pain upper		2		
	Acute abdomen			1	
	Anal fistula	1		1	
	Colitis	1	2		
	Colitis ischaemic		1		
	Constipation		3		
	Diarrhoea	1	1		
	Diverticular perforation		2		
	Diverticulum intestinal			1	
	Duodenal obstruction		1		
	Enterocolitis		1		
	Eosinophilic oesophagitis		1		
	Food poisoning	1			
	Gastritis		2		
	Gastrointestinal haemorrhage	3	4		
	Gastrointestinal mucosa hyperaemia		1		
	Gastrointestinal necrosis		1		
	Gastrooesophageal reflux disease	2			
	Haemorrhoidal haemorrhage		1		

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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;BNT162 B2S01	BLINDED THERAPY	PLACEBO	PRE RANDOMIZATION / NO STUDY DRUG
	Haemorrhoids		1		
	Hiatus hernia		1		
	Ileus		1		
	Impaired gastric emptying		1		
	Incarcerated inguinal hernia		1		
	Inguinal hernia	2		1	
	Intestinal mass			1	
	Intestinal obstruction	2	2		
	Intestinal perforation		2		
	Intestinal strangulation		1		
	Intestinal ulcer perforation	1			
	Large intestine perforation		1		
	Lower gastrointestinal haemorrhage	1	1		
	Obstructive pancreatitis		2		
	Oesophageal food impaction		1		
	Oesophageal varices haemorrhage		1		
	Pancreatic cyst		1		
	Pancreatitis		4		
	Pancreatitis acute	1	5	1	
	Pneumoperitoneum		1		
	Rectal haemorrhage		1		

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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.
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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;BNT162 B2S01	BLINDED THERAPY	PLACEBO	PRE RANDOMIZATION / NO STUDY DRUG
	Retroperitoneal haematoma		1		
	Salivary gland calculus			1	
	Small intestinal obstruction	1	9		
	Splenic artery aneurysm		1		
	Umbilical hernia		1		
	Volvulus		1		
	Vomiting	1			
Sub Total:		**18**	**68**	**7**	
General disorders and administration site conditions	Asthenia		1		
	Chest pain	3	6		
	Condition aggravated	9	23	4	
	Death	2		1	
	Disease progression		1		
	Disease recurrence	2			
	Drug ineffective	1			
	Drug withdrawal syndrome	1	1		
	Electrocution	1			
	Fatigue	1			
	Hypothermia		1		
	Impaired healing		1		
	Influenza like illness		1		
	Multiple organ dysfunction syndrome			1	

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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.
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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	PRE RANDOMIZATION / NO STUDY DRUG
	Non-cardiac chest pain	1	4		
	Pain	1	1		
	Pyrexia		1		
	Shoulder injury related to vaccine administration	1			
	Sudden cardiac death		1		
	Sudden death	1			
	Treatment noncompliance	1			
	Vascular stent occlusion		1		
Sub Total:		**25**	**43**	**6**	
Hepatobiliary disorders	Acute hepatic failure		1		
	Bile duct stone	1	1		
	Biliary colic	1	1		
	Cholecystitis	1	2	1	
	Cholecystitis acute	1	9		
	Cholecystitis chronic		1		
	Cholelithiasis	3	7		
	Cholelithiasis obstructive	1			
	Hepatitis acute	1			
	Hepatocellular injury		1		
	Hyperbilirubinaemia neonatal		1		
	Portal vein thrombosis	1			
	Portosplenomesenteric venous thrombosis	1			

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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.
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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;BNT162 B2S01	BLINDED THERAPY	PLACEBO	PRE RANDOMIZATION / NO STUDY DRUG
Sub Total:		**11**	**24**	**1**	
Immune system disorders	Anaphylactic reaction		1		
	Anaphylactic shock		1		
	Anaphylactoid reaction	1			
	Drug hypersensitivity		1		
	Hypersensitivity		1		
Sub Total:		**1**	**4**		
Infections and infestations	Abdominal abscess		3		
	Abdominal infection	1			
	Abscess		1		
	Abscess limb		1		
	Abscess oral		1		
	Acquired immunodeficiency syndrome	1			
	Anal abscess		2		
	Appendicitis	2	27	3	
	Appendicitis perforated	1	3		
	Arthritis bacterial	1	1		
	Asymptomatic bacteriuria	1			
	Bacteraemia		1		
	Bacterial sepsis	1	1		
	Brain abscess		1		
	Campylobacter gastroenteritis		1		
	Cellulitis		5		

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	Clostridium difficile colitis		1		
	Clostridium difficile infection	1			
	Colonic abscess		1		
	Complicated appendicitis		2		
	COVID-19		12	2	
	COVID-19 pneumonia	1	4		
	Device related infection		1		
	Diabetic foot infection		1		
	Diverticulitis	3	2	1	
	Emphysematous cholecystitis		1		
	Empyema		1		
	Endocarditis		1		
	Escherichia urinary tract infection		1		
	Extradural abscess		1		
	Focal peritonitis	1	1		
	Gangrene		1		
	Gastroenteritis	3	1	1	
	Gastroenteritis bacterial			1	
	Herpes zoster oticus		1		
	HIV infection	1			
	Liver abscess	1	1		
	Localised infection		1		

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SOC	PT	BNT162B2;BNT162 B2S01	BLINDED THERAPY	PLACEBO	PRE RANDOMIZATION / NO STUDY DRUG
	Lower respiratory tract infection	1			
	Meningitis bacterial	1	2		
	Osteomyelitis		1		
	Pelvic abscess	1			
	Pelvic inflammatory disease	1			
	Penile infection	1			
	Peritoneal abscess		1		
	Peritonitis	1	2		
	Peritonsillar abscess		2		
	Pharyngitis streptococcal			1	
	Pneumonia	8	15	1	
	Pneumonia bacterial		1	1	
	Postoperative abscess		1		
	Postoperative wound infection		3		
	Post procedural infection		1	1	
	Pyelonephritis	1	3		
	Pyelonephritis acute		2		
	Renal abscess		1		
	Respiratory syncytial virus bronchiolitis		1		
	Respiratory tract infection viral		1		
	Sepsis	2	8		
	Septic shock		2		
	Shigella sepsis		1		

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SOC	PT	BNT162B2;BNT162 B2S01	BLINDED THERAPY	PLACEBO	PRE RANDOMIZATION / NO STUDY DRUG
	Staphylococcal infection	1	1		
	Staphylococcal sepsis		1		
	Subacute endocarditis			1	
	Subcutaneous abscess		2		
	Suspected COVID-19		1		
	Tooth infection		1		
	Upper respiratory tract infection		2		
	Urinary tract infection	2	9		
	Urosepsis	1	1		
	Wound infection	1			
Sub Total:		**41**	**149**	**13**	
Injury, poisoning and procedural complications	Alcohol poisoning		1		
	Ankle fracture	3	3		
	Brain contusion		1		
	Burns second degree	1			
	Burns third degree	1			
	Cervical vertebral fracture	1	1		
	Clavicle fracture		1		
	Colon injury		1		
	Concussion		1		
	Craniocerebral injury		3		
	Delayed recovery from anaesthesia			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;BNT162 B2S01	BLINDED THERAPY	PLACEBO	PRE RANDOMIZATION / NO STUDY DRUG
	Facial bones fracture	1	2		
	Fall	1	2		
	Femur fracture		3		
	Fibula fracture	1			
	Flail chest		1		
	Foot fracture	1	1	1	
	Forearm fracture		1		
	Fractured sacrum		1		
	Hand fracture		1		
	Head injury	1	2		
	Hip fracture		2	1	
	Humerus fracture		1	1	
	Injury		1		
	Jaw fracture	1			
	Joint dislocation	1			
	Ligament rupture	1	1		
	Limb injury	1			
	Lower limb fracture		2	1	
	Lumbar vertebral fracture		1		
	Maternal exposure during pregnancy	1	11		
	Meniscus injury		2		
	Multiple injuries		1		
	Overdose	2	3		
	Patella fracture		1		
	Pelvic fracture	1	1		
	Postoperative ileus		1		

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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;BNT162 B2S01	BLINDED THERAPY	PLACEBO	PRE RANDOMIZATION / NO STUDY DRUG
	Post procedural haematoma		1		
	Post-traumatic pain		1		
	Procedural dizziness	1			
	Procedural haemorrhage		1		
	Procedural pain	1			
	Radius fracture			1	
	Rib fracture	3	2		
	Road traffic accident	1	8		
	Scapula fracture	1			
	Spinal column injury		1		
	Spinal cord injury cervical		1		
	Spinal fracture	1			
	Splenic rupture		1		
	Subdural haematoma		3		
	Tibia fracture	1	1		
	Toxicity to various agents		3		
	Traumatic haemothorax		1		
	Traumatic intracranial haemorrhage		1		
	Ulna fracture	1	1		
	Upper limb fracture	1	1		
	Venous injury		1		
	Wrist fracture		3		
Sub Total:		**30**	**85**	**6**	

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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	PRE RANDOMIZATION / NO STUDY DRUG
Investigations	Alanine aminotransferase increased	1			
	Aspartate aminotransferase increased	1			
	Blood glucose abnormal		1		
	Blood lactic acid	1			
	Blood pressure increased		1		
	Foetal heart rate abnormal		1		
	Hepatic enzyme increased		1		
Sub Total:		**3**	**4**		
Metabolism and nutrition disorders	Dehydration	1	1		
	Diabetes mellitus inadequate control		1		
	Diabetic ketoacidosis	2	3		
	Fluid retention		1		
	Gout		1		
	Hyperglycaemia	1	1	1	
	Hypernatraemia		1		
	Hypoglycaemia	1	3		
	Hypokalaemia	2	2		
	Hyponatraemia	1	3		
	Malnutrition		1		
	Metabolic acidosis		1		
	Obesity	1			

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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;BNT162 B2S01	BLINDED THERAPY	PLACEBO	PRE RANDOMIZATION / NO STUDY DRUG
	Type 2 diabetes mellitus	1	3		
Sub Total:		**10**	**22**	**1**	
Musculoskeletal and connective tissue disorders	Arthralgia		2		
	Arthritis	1	1		
	Back pain	2		1	
	Intervertebral disc compression		1		
	Intervertebral disc degeneration	1	2	2	
	Intervertebral disc protrusion		4		1
	Lumbar spinal stenosis	2			
	Muscular weakness		3		
	Musculoskeletal chest pain		1		
	Myalgia	1			
	Osteoarthritis	5	6	2	
	Osteochondritis		1		
	Pain in extremity		1		
	Polymyalgia rheumatica	1			
	Psoriatic arthropathy			1	
	Spinal stenosis			1	
	Spondylolisthesis		2	1	
Sub Total:		**13**	**24**	**8**	**1**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Acute myeloid leukaemia	1	1		

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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	PRE RANDOMIZATION / NO STUDY DRUG
	Adenocarcinoma gastric		1		
	Adenocarcinoma of colon	1	1		
	Adenocarcinoma pancreas	1	2		
	Adrenal gland cancer		1		
	Basal cell carcinoma	1		2	
	B-cell lymphoma		1		
	Benign hydatidiform mole		1		
	Biliary cancer metastatic		1		
	Bladder cancer		2		
	Borderline serous tumour of ovary	1			
	Brain neoplasm	1			
	Breast cancer	4	5	3	
	Breast cancer in situ		1		
	Breast cancer metastatic	1			
	Breast cancer stage I	1	1		
	Chronic myeloid leukaemia		1		
	Clear cell renal cell carcinoma			1	
	Colon adenoma		1		
	Endometrial adenocarcinoma	2			
	Gallbladder cancer stage II		1		
	Gastric cancer	1		1	

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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;BNT162 B2S01	BLINDED THERAPY	PLACEBO	PRE RANDOMIZATION / NO STUDY DRUG
	Glioblastoma	1			
	Hepatic cancer	1			
	Hepatic cancer metastatic		1		
	Hormone receptor positive breast cancer	1	1		
	Hypergammaglobulinaemia benign monoclonal	1			
	Intraductal proliferative breast lesion	1	2		
	Invasive ductal breast carcinoma	4	3		
	Invasive lobular breast carcinoma	1	1		
	Leydig cell tumour of the testis		1		
	Lipoma		1		
	Lung adenocarcinoma	1		2	
	Lung cancer metastatic		2		
	Malignant melanoma		5	1	
	Meningioma		1		
	Metastases to central nervous system	1	1		
	Metastases to liver		1		
	Metastases to lung		1		
	Metastases to lymph nodes		1	1	

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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;BNT162 B2S01	BLINDED THERAPY	PLACEBO	PRE RANDOMIZATION / NO STUDY DRUG
	Metastatic gastric cancer	1			
	Metastatic malignant melanoma	1			
	Metastatic squamous cell carcinoma		2		
	Neoplasm recurrence	1			
	Non-Hodgkin's lymphoma recurrent			1	
	Non-small cell lung cancer stage III	1			
	Non-small cell lung cancer stage IV		1		
	Oesophageal adenocarcinoma	1			
	Oropharyngeal cancer recurrent			1	
	Oropharyngeal squamous cell carcinoma		1		
	Ovarian cancer	1			
	Ovarian neoplasm	1			
	Pancreatic carcinoma	1	1	1	
	Pancreatic carcinoma metastatic		1		
	Pancreatic neuroendocrine tumour		1		
	Papillary serous endometrial carcinoma			1	
	Papillary thyroid cancer			1	

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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.
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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;BNT162 B2S01	BLINDED THERAPY	PLACEBO	PRE RANDOMIZATION / NO STUDY DRUG
	Penile neoplasm		1		
	Plasma cell myeloma		1		
	Polycythaemia vera			1	
	Prostate cancer		5		
	Prostate cancer metastatic	1			
	Renal neoplasm		1		
	Sebaceous carcinoma		1		
	Seminoma		1		
	Squamous cell carcinoma	1			
	Teratoma			1	
	Testis cancer		1		
	Thyroid cancer	1			
	Tonsil cancer		1		
	Transitional cell carcinoma	1		1	
	Transitional cell carcinoma recurrent	1			
	Uterine cancer		1		
	Uterine leiomyoma	1	4	1	
Sub Total:		**41**	**67**	**20**	
Nervous system disorders	Amnesia		1		
	Amyotrophic lateral sclerosis			1	
	Aphasia	2			
	Brachial plexopathy	1			
	Carotid artery stenosis	1			

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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.
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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	PRE RANDOMIZATION / NO STUDY DRUG
	Carpal tunnel syndrome		1		
	Cerebral infarction		1		
	Cerebrovascular accident	10	6	2	
	Cervical radiculopathy	1			
	Cervicogenic headache		1		
	Dementia Alzheimer's type		1	1	
	Dizziness		3		
	Encephalopathy	1			
	Guillain-Barre syndrome			1	
	Haemorrhagic stroke		2		
	Hemiplegic migraine		1		
	Hypoaesthesia		1		
	Hypoxic-ischaemic encephalopathy		1		
	Idiopathic intracranial hypertension	1	1		
	Intracranial aneurysm		1		
	Intraventricular haemorrhage		1		
	Ischaemic stroke	2	4		
	Myasthenia gravis	1			
	Neuritis		1		
	Neuropathy peripheral		1		
	Optic neuritis	1	1		

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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;BNT162 B2S01	BLINDED THERAPY	PLACEBO	PRE RANDOMIZATION / NO STUDY DRUG
	Paraesthesia	1	1		
	Peripheral nerve lesion	1			
	Presyncope	2			
	Psychogenic seizure	1			
	Seizure	2	1		
	Spinal cord compression		1	1	
	Status migrainosus	1			
	Subarachnoid haemorrhage	1	4	1	
	Syncope	3	7	1	
	Toxic encephalopathy	1	1		
	Transient global amnesia		1		
	Transient ischaemic attack	3	5		
	Uraemic encephalopathy		1		
Sub Total:		**37**	**51**	**8**	
Pregnancy, puerperium and perinatal conditions	Abortion incomplete			1	
	Abortion spontaneous	4	10	3	
	Abortion spontaneous incomplete		1		
	Foetal hypokinesia		1		
	Hyperemesis gravidarum		1		
	Pre-eclampsia		1		

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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;BNT162 B2S01	BLINDED THERAPY	PLACEBO	PRE RANDOMIZATION / NO STUDY DRUG
	Premature separation of placenta		1		
	Retained products of conception		1		
Sub Total:		**4**	**16**	**4**	
Psychiatric disorders	Acute psychosis	1			
	Affective disorder		1		
	Alcohol abuse		1		
	Alcoholism		1		
	Alcohol withdrawal syndrome		2		
	Anxiety	2			
	Bipolar disorder	1	3		
	Bipolar I disorder	1			
	Completed suicide	2	1		
	Conversion disorder		2		
	Depression	2	8	1	
	Depression suicidal		1	1	
	Disorientation	1			
	Drug abuse	1			
	Drug dependence		2		
	Major depression	5	2		
	Mental disorder		1		
	Panic attack		1		
	Psychotic disorder		2		
	Suicidal ideation	3	6	1	
	Suicide attempt	2	1	1	
Sub Total:		**21**	**35**	**4**	

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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;BNT162 B2S01	BLINDED THERAPY	PLACEBO	PRE RANDOMIZATION / NO STUDY DRUG
Renal and urinary disorders	Acute kidney injury	2	2		
	Hydronephrosis			1	
	Nephrolithiasis	2	15		
	Renal colic		1		
	Renal tubular necrosis		1		
	Renal vein thrombosis		1		
	Subcapsular renal haematoma		1		
	Ureterolithiasis		3		
	Urinary tract obstruction	1			
Sub Total:		**5**	**24**	**1**	
Reproductive system and breast disorders	Adenomyosis		1		
	Adnexal torsion		1	1	
	Breast hyperplasia		1		
	Endometrial thickening		1		
	Endometriosis		2		
	Infertility	1			
	Ovarian cyst		2		
	Ovarian mass		1		
	Rectocele			1	
	Uterine prolapse		1		
	Vaginal haemorrhage		1		
	Vaginal prolapse			1	
Sub Total:		**1**	**11**	**3**	

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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;BNT162 B2S01	BLINDED THERAPY	PLACEBO	PRE RANDOMIZATION / NO STUDY DRUG
Respiratory, thoracic and mediastinal disorders	Acute respiratory failure	5	5		
	Asphyxia		1		
	Asthma	1	3		
	Asthmatic crisis		1		
	Chronic obstructive pulmonary disease	1	6		
	Dyspnoea	1	4		
	Dyspnoea exertional		2		
	Hypoxia		1		
	Interstitial lung disease		2		
	Nasal septum deviation		1		
	Neonatal pneumothorax		1		
	Neonatal respiratory failure		1		
	Pleural effusion	2			
	Pneumonia aspiration	1	3		
	Pneumonitis		1		
	Pneumothorax	2	1		
	Pulmonary embolism	10	9	2	
	Pulmonary mass		1		
	Respiratory arrest		1		
	Respiratory failure	1	2		
Sub Total:		**24**	**46**	**2**	
Skin and subcutaneous tissue disorders	Diabetic foot	1			
	Pruritus		1		

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Treatment Grouping:
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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;BNT162 B2S01	BLINDED THERAPY	PLACEBO	PRE RANDOMIZATION / NO STUDY DRUG
Sub Total:		**1**	**1**		
Social circumstances	Miscarriage of partner		1		
Sub Total:			**1**		
Surgical and medical procedures	Myomectomy		1		
Sub Total:			**1**		
Vascular disorders	Accelerated hypertension		1		
	Aortic aneurysm		2		
	Aortic rupture		2		
	Aortic stenosis	1		2	
	Arteriosclerosis	1	2		
	Deep vein thrombosis	4	7	1	
	Embolism	1			
	Hypertension	3	3		
	Hypertensive crisis		1		
	Hypertensive emergency	3	1		
	Hypertensive urgency	2	2		
	Hypotension		1		
	Hypovolaemic shock	1			
	Iliac artery dissection		1		
	Orthostatic hypotension		2		
	Peripheral artery stenosis		1		
	Shock		1		
	Thrombosis	1			

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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;BNT162 B2S01	BLINDED THERAPY	PLACEBO	PRE RANDOMIZATION / NO STUDY DRUG
	Venous thrombosis limb	1			
Sub Total:		**18**	**27**	**3**	
Total Number of Cases:		**297**	**650**	**82**	**1**
Total Number of Events:		**364**	**822**	**98**	**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.

APPENDIX 2.1.1 - Cumulative Summary Tabulation of Serious Adverse Events from Clinical Trials

BNT162B2

Reporting Period: Through 18-JUN-2021
Total Number of Cases: 18
Total Number of Adverse Events (PT): 21
MedDRA Version: v.24.0J

SOC	PT	BNT162B2;BNT162B2S01	BLINDED THERAPY	COMPARATOR
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		
Sub Total:		**2**		
General disorders and administration site conditions	Disease progression		1	
	Pelvic mass			1
Sub Total:			**1**	**1**
Hepatobiliary disorders	Cholecystitis acute		1	
Sub Total:			**1**	
Infections and infestations	COVID-19			2
	Cystitis	1		
Sub Total:		**1**		**2**

* 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;BNT162 B2S01	BLINDED THERAPY	COMPARATOR
Injury, poisoning and procedural complications	Ankle fracture	1		
	Humerus fracture		1	
	Joint dislocation		1	
	Lower limb fracture		1	
Sub Total:		**1**	**3**	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Lung carcinoma cell type unspecified stage 0		1	
	Oesophageal carcinoma	1		
Sub Total:		**1**	**1**	
Nervous system disorders	Cerebral infarction		2	
	Diabetic neuropathy		1	
	Syncope			1
Sub Total:			**3**	**1**
Total Number of Cases:		**5**	**8**	**5**
Total Number of Events:		**5**	**10**	**6**

* 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 2.2: Cumulative and Interval Summary Tabulation of Serious and Non-Serious Adverse Reactions from Post-Marketing Data Sources

BNT162B2

Cumulative Reporting Period: Through 18-JUN-2021

Interval Reporting Period: 19-DEC-2020 Through 18-JUN-2021

Total Number of Cases: 327,125 (Interval) / 327,603 (Cumulative)

Total Number of Adverse Events (PT): 1,171,013 (Interval) / 1,172,396 (Cumulative)

MedDRA Version: v.24.0J

System Organ Class

Blood and lymphatic system disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Abdominal lymphadenopathy	4	2	2	2	2		
Abnormal clotting factor	5	4	4	1	1		
Acquired haemophilia	9	9	9			1	1
Agranulocytosis	7	7	7				
Anaemia	205	135	135	70	70	1	1
Anaemia macrocytic	5	5	5				
Anaemia megaloblastic	1	1	1				
Anaemia vitamin B12 deficiency	3	1	1	2	2		
Anisocytosis	4	2	2	2	2		
Antiphospholipid syndrome	8	8	8				
Aplasia pure red cell	3	3	3				
Aplastic anaemia	1	1	1				
Atypical haemolytic uraemic syndrome	1	1	1				
Autoimmune anaemia	2	2	2				
Autoimmune haemolytic anaemia	20	20	20				
Autoimmune neutropenia	3	3	3				
Bicytopenia	6	5	5	1	1		
Blood disorder	25	8	8	17	17		
Blood loss anaemia	4	4	4				

* I=Interval, C=Cumulative
* AE=Adverse Event
* Multiple adverse events coding to the same Preferred Term may have been reported in some cases. Counts are provided for the number of unique Preferred Terms reported.

System Organ Class

Blood and lymphatic system disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Bone marrow disorder	6	2	2	4	4		
Bone marrow failure	1	1	1				
Bone marrow oedema	3	2	2	1	1		
Coagulopathy	113	79	79	34	34		
Coombs negative haemolytic anaemia	4	4	4				
Coombs positive haemolytic anaemia	1	1	1				
Deficiency anaemia	1			1	1		
Disseminated intravascular coagulation	14	14	14				
Eosinophilia	34	24	24	10	10		
Erythropenia	2	1	1	1	1		
Evans syndrome	2	2	2				
Factor VIII inhibition	1	1	1				
Febrile bone marrow aplasia	1	1	1				
Febrile neutropenia	6	6	6				
Granulocytopenia	1	1	1				
Haemoconcentration	1			1	1		
Haemoglobinaemia	2	1	1	1	1		
Haemolysis	14	14	14				
Haemolytic anaemia	27	27	27				
Haemolytic uraemic syndrome	2	2	2				
Haemorrhagic diathesis	17	17	17				
Haemorrhagic disorder	17	17	17				
Heparin-induced thrombocytopenia	1	1	1				
Hilar lymphadenopathy	3	1	1	2	2		
Hyperchromic anaemia	2	2	2				
Hypercoagulation	9	8	8	1	1		
Hypereosinophilic syndrome	2	2	2				

* I=Interval, C=Cumulative
* AE=Adverse Event
* Multiple adverse events coding to the same Preferred Term may have been reported in some cases. Counts are provided for the number of unique Preferred Terms reported.

System Organ Class

Blood and lymphatic system disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Hyperfibrinogenaemia	1	1	1				
Hypergammaglobulinaemia	1			1	1		
Hyperleukocytosis	26	26	26				
Hyperviscosity syndrome	1	1	1				
Hypochromasia	2			2	2		
Hypochromic anaemia	3	3	3				
Hypocoagulable state	1			1	1		
Immune thrombocytopenia	200	199	199	1	1	1	1
Increased tendency to bruise	29	12	12	17	17		
Intravascular haemolysis	1	1	1				
Iron deficiency anaemia	12	8	8	4	4		
Leukaemoid reaction	1	1	1				
Leukocytosis	62	40	40	22	22	1	1
Leukopenia	50	50	50			1	1
Lymphadenitis	570	139	139	431	431		
Lymphadenopathy	18522	3597	3599	14917	14923	29	29
Lymphadenopathy mediastinal	7	3	3	4	4		
Lymphatic disorder	7	1	1	6	6		
Lymphatic obstruction	1	1	1				
Lymph node pain	2311	691	692	1618	1619	9	9
Lymph node rupture	1			1	1		
Lymphocytic infiltration	1	1	1				
Lymphocytosis	13	5	5	8	8		
Lymphoid tissue hyperplasia	1			1	1		
Lymphopenia	73	37	37	36	36		
Mast cell activation syndrome	7	7	7				
Mastocytosis	3	1	1	2	2		

* I=Interval, C=Cumulative
* AE=Adverse Event
* Multiple adverse events coding to the same Preferred Term may have been reported in some cases. Counts are provided for the number of unique Preferred Terms reported.

System Organ Class

Blood and lymphatic system disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Methaemoglobinaemia	1	1	1				
Microangiopathic haemolytic anaemia	3	3	3				
Microcytic anaemia	4	3	3	1	1		
Microcytosis	1			1	1		
Monocytosis	15	5	5	10	10		
Myelocytosis	1	1	1				
Myelosuppression	5	5	5				
Necrotic lymphadenopathy	3	3	3				
Neutropenia	77	76	77			1	1
Neutropenia neonatal	1	1	1				
Neutrophilia	16	9	9	7	7		
Normochromic anaemia	1	1	1				
Normochromic normocytic anaemia	5	2	2	3	3		
Normocytic anaemia	5	2	2	3	3		
Nucleated red cells	2			2	2		
Pancytopenia	37	37	37				
Paratracheal lymphadenopathy	6	2	2	4	4		
Platelet anisocytosis	1	1	1				
Platelet disorder	10	5	5	5	5		
Poikilocytosis	1			1	1		
Polychromasia	2	2	2				
Polycythaemia	3	1	1	2	2		
Pseudolymphoma	6	2	2	4	4		
Purpura non-thrombocytopenic	3	3	3				
Red blood cell abnormality	3	1	1	2	2	1	1
Reticulocytosis	1	1	1				
Retroperitoneal lymphadenopathy	1	1	1				

* I=Interval, C=Cumulative
* AE=Adverse Event
* Multiple adverse events coding to the same Preferred Term may have been reported in some cases. Counts are provided for the number of unique Preferred Terms reported.

System Organ Class

Blood and lymphatic system disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Secondary thrombocytosis	1	1	1				
Sickle cell anaemia with crisis	4	4	4				
Spleen atrophy	1	1	1				
Spleen disorder	5	2	2	3	3		
Splenic artery thrombosis	1	1	1				
Splenic cyst	2			2	2		
Splenic haemorrhage	1	1	1				
Splenic infarction	14	14	14				
Splenic necrosis	1	1	1				
Splenic thrombosis	1	1	1				
Splenic vein thrombosis	10	10	10				
Splenitis	1	1	1				
Splenomegaly	21	15	15	6	6		
Spontaneous haematoma	13	9	9	4	4	1	1
Thrombocytopenia	536	529	529	7	7	2	2
Thrombocytopenic purpura	27	23	23	4	4		
Thrombocytosis	17	11	11	6	6		
Thrombotic microangiopathy	8	8	8				
Thrombotic thrombocytopenic purpura	16	16	16				
White blood cell disorder	5	3	3	2	2		
Total:	23409	6096	6100	17302	17309	48	48

System Organ Class

Cardiac disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Abnormal precordial movement	1			1	1		

* I=Interval, C=Cumulative
* AE=Adverse Event
* Multiple adverse events coding to the same Preferred Term may have been reported in some cases. Counts are provided for the number of unique Preferred Terms reported.

System Organ Class

Cardiac disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Acute cardiac event	7	7	7				
Acute coronary syndrome	84	84	84				
Acute left ventricular failure	3	3	3				
Acute myocardial infarction	265	264	265				
Acute right ventricular failure	1	1	1				
Angina pectoris	343	328	328	15	15		
Angina unstable	10	10	10				
Aortic valve calcification	3	3	3				
Aortic valve disease	1	1	1				
Aortic valve incompetence	7	7	7				
Aortic valve sclerosis	1			1	1		
Aortic valve stenosis	7	7	7				
Arrhythmia	771	737	737	34	34	2	2
Arrhythmia supraventricular	20	17	17	3	3		
Arteriosclerosis coronary artery	15	12	12	3	3		
Arteriospasm coronary	8	8	8				
Atrial fibrillation	878	870	870	8	8	4	5
Atrial flutter	63	48	48	15	15		
Atrial tachycardia	15	10	10	5	5	1	1
Atrial thrombosis	5	5	5				
Atrioventricular block	25	24	24	1	1	2	2
Atrioventricular block complete	32	32	32			1	1
Atrioventricular block first degree	6	3	3	3	3		
Atrioventricular block second degree	11	9	9	2	2		
Autoimmune myocarditis	1	1	1				
Bezold-Jarisch reflex	1			1	1		
Bradyarrhythmia	4	3	3	1	1		

* I=Interval, C=Cumulative
* AE=Adverse Event
* Multiple adverse events coding to the same Preferred Term may have been reported in some cases. Counts are provided for the number of unique Preferred Terms reported.

System Organ Class

Cardiac disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Bradycardia	361	354	354	7	7	5	5
Bradycardia foetal	1	1	1				
Bundle branch block	5	3	3	2	2		
Bundle branch block left	16	11	11	5	5		
Bundle branch block right	33	24	24	9	9		
Cardiac amyloidosis	3	3	3				
Cardiac aneurysm	1	1	1				
Cardiac arrest	474	470	471	3	3	1	1
Cardiac asthma	7	7	7				
Cardiac discomfort	48	16	16	32	32		
Cardiac disorder	227	113	113	114	114		
Cardiac dysfunction	6	6	6				
Cardiac failure	484	481	481	3	3	1	1
Cardiac failure acute	66	65	65	1	1		
Cardiac failure chronic	11	11	11				
Cardiac failure congestive	67	67	67				
Cardiac fibrillation	27	25	25	2	2		
Cardiac flutter	177	173	173	4	4		
Cardiac hypertrophy	11	8	8	3	3		
Cardiac sarcoidosis	1	1	1				
Cardiac tamponade	21	21	21				
Cardiac valve disease	10	9	9	1	1		
Cardiac valve sclerosis	1	1	1				
Cardiac ventricular thrombosis	4	4	4				
Cardiogenic shock	57	57	57				
Cardiomegaly	39	21	21	18	18		
Cardiomyopathy	26	26	26				

* I=Interval, C=Cumulative
* AE=Adverse Event
* Multiple adverse events coding to the same Preferred Term may have been reported in some cases. Counts are provided for the number of unique Preferred Terms reported.

System Organ Class

Cardiac disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Cardiopulmonary failure	30	30	30				
Cardio-respiratory arrest	226	224	224	2	2		
Cardio-respiratory distress	3	3	3				
Cardiovascular disorder	302	122	122	180	180		
Cardiovascular insufficiency	17	17	17				
Cardiovascular symptom	2	1	1	1	1		
Carditis	1	1	1				
Conduction disorder	2	1	1	1	1		
Congestive cardiomyopathy	7	7	7				
Coronary artery disease	34	31	31	3	3		
Coronary artery dissection	3	3	3				
Coronary artery insufficiency	1	1	1				
Coronary artery occlusion	20	20	20			2	2
Coronary artery stenosis	24	24	24				
Coronary artery thrombosis	23	23	23				
Coronary ostial stenosis	1	1	1				
Cor pulmonale	5	5	5				
Cor pulmonale acute	5	5	5				
Defect conduction intraventricular	3	3	3				
Degenerative mitral valve disease	1	1	1				
Diastolic dysfunction	1	1	1				
Dilatation atrial	4	4	4				
Dilatation ventricular	6	3	3	3	3		
Extrasystoles	267	122	122	145	145	1	1
Foetal heart rate disorder	1	1	1				
Heart alternation	2	1	1	1	1		
Heart valve incompetence	4	2	2	2	2		

* I=Interval, C=Cumulative
* AE=Adverse Event
* Multiple adverse events coding to the same Preferred Term may have been reported in some cases. Counts are provided for the number of unique Preferred Terms reported.

System Organ Class

Cardiac disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Hepatojugular reflux	2			2	2		
Hyperdynamic left ventricle	1	1	1				
Hypertensive heart disease	12	12	12				
Interventricular septum rupture	1	1	1				
Intracardiac thrombus	23	23	23				
Ischaemic cardiomyopathy	4	4	4				
Left atrial dilatation	4	3	3	1	1		
Left ventricular dilatation	2			2	2		
Left ventricular dysfunction	11	9	9	2	2		
Left ventricular failure	21	21	21				
Left ventricular hypertrophy	15	10	10	5	5		
Long QT syndrome	1	1	1				
Microvascular coronary artery disease	3	3	3				
Mitral valve calcification	3	3	3				
Mitral valve disease	2	2	2				
Mitral valve incompetence	21	21	21				
Mitral valve prolapse	3	2	2	1	1		
Mitral valve stenosis	3	3	3				
Myocardial calcification	1			1	1		
Myocardial fibrosis	4	3	3	1	1		
Myocardial haemorrhage	1	1	1				
Myocardial hypoxia	2	2	2				
Myocardial infarction	630	626	626	4	4	3	3
Myocardial ischaemia	60	60	60				
Myocardial necrosis	1	1	1				
Myocardial oedema	4	4	4				
Myocardial rupture	6	6	6				

* I=Interval, C=Cumulative
* AE=Adverse Event
* Multiple adverse events coding to the same Preferred Term may have been reported in some cases. Counts are provided for the number of unique Preferred Terms reported.

System Organ Class

Cardiac disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Myocarditis	502	495	495	7	7		
Nodal arrhythmia	2	1	1	1	1		
Nodal rhythm	4	2	2	2	2		
Palpitations	4407	1730	1733	2668	2674	8	8
Paroxysmal arrhythmia	2	2	2				
Paroxysmal atrioventricular block	1	1	1				
Pericardial cyst	1			1	1		
Pericardial disease	2	1	1	1	1		
Pericardial effusion	133	130	130	3	3	2	2
Pericardial haemorrhage	9	9	9				
Pericardial rub	1	1	1				
Pericarditis	363	360	360	3	3	1	1
Pleuropericarditis	12	12	12				
Postural orthostatic tachycardia syndrome	34	25	25	9	9	1	1
Prinzmetal angina	3	2	2	1	1		
Pulseless electrical activity	11	11	11				
Restrictive cardiomyopathy	1	1	1				
Rhythm idioventricular	1	1	1				
Right atrial enlargement	1			1	1		
Right ventricular dilatation	6	3	3	3	3		
Right ventricular dysfunction	7	7	7				
Right ventricular enlargement	3	1	1	2	2		
Right ventricular failure	15	15	15				
Right ventricular hypertrophy	1	1	1				
Sinoatrial block	2	2	2				
Sinus arrest	4	4	4				
Sinus arrhythmia	5	1	1	4	4		

* I=Interval, C=Cumulative
* AE=Adverse Event
* Multiple adverse events coding to the same Preferred Term may have been reported in some cases. Counts are provided for the number of unique Preferred Terms reported.

System Organ Class

Cardiac disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Sinus bradycardia	21	13	13	8	8		
Sinus node dysfunction	3	3	3				
Sinus tachycardia	195	113	113	82	82	1	1
Stress cardiomyopathy	22	21	21	1	1		
Supraventricular extrasystoles	47	25	25	22	22		
Supraventricular tachyarrhythmia	4	2	2	2	2		
Supraventricular tachycardia	100	76	79	21	21		
Systolic dysfunction	4	4	4				
Tachyarrhythmia	53	31	31	22	22	1	1
Tachycardia	6228	1853	1858	4367	4370	16	16
Tachycardia foetal	1	1	1				
Tachycardia induced cardiomyopathy	1	1	1				
Tachycardia paroxysmal	21	10	10	11	11	1	1
Torsade de pointes	2	2	2				
Tricuspid valve incompetence	12	12	12				
Ventricle rupture	1	1	1				
Ventricular arrhythmia	17	17	17				
Ventricular dysfunction	3	2	2	1	1		
Ventricular extrasystoles	149	77	78	69	71		
Ventricular failure	1	1	1				
Ventricular fibrillation	54	54	54				
Ventricular flutter	1	1	1				
Ventricular hypertrophy	5	4	4	1	1		
Ventricular hypokinesia	8	8	8				
Ventricular tachycardia	55	55	55				
Wandering pacemaker	1	1	1				
Total:	19150	11158	11172	7967	7978	54	55

* I=Interval, C=Cumulative
* AE=Adverse Event
* Multiple adverse events coding to the same Preferred Term may have been reported in some cases. Counts are provided for the number of unique Preferred Terms reported.

System Organ Class

Congenital, familial and genetic disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Amegakaryocytic thrombocytopenia	2	2	2				
Anencephaly	2	2	2				
Ankyloglossia congenital	1	1	1				
Anomalous pulmonary venous connection	1	1	1				
Antithrombin III deficiency	1	1	1				
Aplasia	1	1	1				
Argininosuccinate synthetase deficiency	1			1	1		
Arnold-Chiari malformation	2	2	2				
Arteriovenous malformation	1	1	1				
Atrial septal defect	2	2	2				
Block vertebra	1	1	1				
Cerebral palsy	6	6	6				
Cleft palate	1	1	1				
Colour blindness	2			2	2		
Congenital absence of cranial vault	1	1	1				
Congenital anomaly	3	3	3				
Congenital cystic kidney disease	1	1	1				
Congenital cystic lung	1	1	1				
Congenital methaemoglobinaemia	1	1	1				
Corneal dystrophy	1	1	1				
Craniosynostosis	1	1	1				
Cystic lymphangioma	3	3	3				
Dermoid cyst	1	1	1				
Ductus arteriosus premature closure	1	1	1				
Dysmorphism	2	1	1	1	1		
Ehlers-Danlos syndrome	2	2	2				
Elliptocytosis hereditary	1	1	1				

* I=Interval, C=Cumulative
* AE=Adverse Event
* Multiple adverse events coding to the same Preferred Term may have been reported in some cases. Counts are provided for the number of unique Preferred Terms reported.

System Organ Class

Congenital, familial and genetic disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Factor II mutation	1			1	1		
Factor V deficiency	1	1	1				
Factor VIII deficiency	1	1	1				
Factor V Leiden mutation	2	1	1	1	1		
Familial hemiplegic migraine	2	2	2				
Familial mediterranean fever	2	2	2				
Familial periodic paralysis	1	1	1				
Foetal cystic hygroma	3	3	3				
Foetal malformation	2	1	1	1	1		
Gastrointestinal malformation	2	2	2				
Gastroschisis	1	1	1				
Gene mutation	1			1	1		
Gilbert's syndrome	2	1	1	1	1		
Haemophilia	3	2	2	1	1		
Hamartoma	1	1	1				
Heart disease congenital	5	5	5				
Hereditary angioedema	1	1	1				
Hereditary angioedema with normal C1 esterase inhibitor	1	1	1				
Hereditary ataxia	1	1	1				
Hereditary haemorrhagic telangiectasia	1			1	1		
Hereditary neuropathy with liability to pressure palsies	1	1	1				
Huntington's disease	6	4	4	2	2		
Hydrocele	1			1	1		
Hyperexplexia	2			2	2		
Hyperglycinaemia	2	1	1	1	1		
Hypertrophic cardiomyopathy	7	7	7				
Kidney duplex	1	1	1				

* I=Interval, C=Cumulative
* AE=Adverse Event
* Multiple adverse events coding to the same Preferred Term may have been reported in some cases. Counts are provided for the number of unique Preferred Terms reported.

System Organ Class

Congenital, familial and genetic disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Klippel-Trenaunay syndrome	1	1	1				
Macrocephaly	1	1	1				
Macroglossia	13	13	13			1	1
Methylenetetrahydrofolate reductase gene mutation	1			1	1		
Moebius II syndrome	1	1	1				
Muscular dystrophy	1			1	1		
Myoclonic dystonia	2	2	2				
Neurofibromatosis	1	1	1				
Osteogenesis imperfecta	1	1	1				
Parkes-Weber syndrome	1			1	1		
Porphyria	1	1	1				
Porphyria acute	1	1	1				
Preauricular cyst	1	1	1				
PTEN gene mutation	1	1	1				
Retinitis pigmentosa	2	2	2				
Rippling muscle disease	1			1	1		
Sensory neuropathy hereditary	1	1	1				
Sickle cell trait	1			1	1		
Spina bifida	1	1	1				
Spine malformation	1	1	1				
Syndactyly	2	2	2				
Thalassaemia minor	1	1	1				
Thyroglossal cyst	1	1	1				
Tourette's disorder	1	1	1				
Transposition of the great vessels	1	1	1				
Trisomy 21	3	2	2	1	1		
Type V hyperlipidaemia	2	2	2				

* I=Interval, C=Cumulative
* AE=Adverse Event
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System Organ Class

Congenital, familial and genetic disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Ventricular septal defect	1	1	1				
Von Willebrand's disease	2	2	2				
Williams syndrome	1	1	1				
Total:	146	123	123	23	23	1	1

System Organ Class

Ear and labyrinth disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Acute vestibular syndrome	14	10	10	4	4		
Auditory disorder	36	14	14	22	22		
Auricular chondritis	1			1	1		
Auricular swelling	12	5	5	7	7		
Autophony	2	1	1	1	1		
Cerumen impaction	2			2	2		
Conductive deafness	4	4	4				
Deafness	394	378	379	15	15		
Deafness bilateral	20	20	20				
Deafness neurosensory	66	66	66				
Deafness transitory	14	13	13	1	1		
Deafness unilateral	185	181	181	4	4	1	1
Dysacusis	5	2	2	3	3		
Ear canal erythema	3	1	1	2	2		
Ear congestion	50	17	17	33	33		
Ear discomfort	474	121	121	353	353		
Ear disorder	89	20	20	69	69		
Ear haemorrhage	20	8	8	12	12		

* I=Interval, C=Cumulative
* AE=Adverse Event
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System Organ Class

Ear and labyrinth disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Ear pain	1444	468	468	976	976		
Ear pruritus	90	24	24	66	66		
Ear swelling	115	36	36	79	79	1	1
Endolymphatic hydrops	4	3	3	1	1		
Eustachian tube disorder	3	2	2	1	1		
Eustachian tube dysfunction	12	4	4	8	8		
Eustachian tube obstruction	5	1	1	4	4		
Excessive cerumen production	11	5	5	6	6		
External ear disorder	2	1	1	1	1		
External ear inflammation	5	2	2	3	3		
External ear pain	12	3	3	9	9		
Hyperacusis	134	51	51	83	83		
Hypoacusis	438	170	170	268	268	1	1
Inner ear disorder	21	13	13	8	8		
Inner ear inflammation	8	5	5	3	3		
Mastoid disorder	2	1	1	1	1		
Meniere's disease	41	38	38	3	3		
Middle ear disorder	3	2	2	1	1		
Middle ear effusion	5	2	2	3	3		
Middle ear inflammation	3	1	1	2	2		
Misophonia	5	3	3	2	2		
Motion sickness	72	32	32	40	40		
Neurosensory hypoacusis	10	7	7	3	3	1	1
Otolithiasis	3	2	2	1	1		
Otorrhoea	11	2	2	9	9		
Paraesthesia ear	18	5	5	13	13		
Phobic postural vertigo	3			3	3		

* I=Interval, C=Cumulative
* AE=Adverse Event
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System Organ Class

Ear and labyrinth disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Presbyacusis	2	1	1	1	1		
Red ear syndrome	5			5	5		
Sudden hearing loss	132	126	126	6	6		
Tinnitus	2559	979	980	1576	1579	5	5
Tympanic membrane disorder	2			2	2		
Tympanic membrane hyperaemia	2	1	1	1	1		
Tympanic membrane perforation	3	2	2	1	1		
Vertigo	3970	1150	1150	2819	2820	8	8
Vertigo labyrinthine	8	6	6	2	2		
Vertigo positional	146	76	76	70	70	1	1
Vestibular disorder	33	13	13	20	20		
Total:	10733	4098	4100	6629	6633	18	18

System Organ Class

Endocrine disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous			
		Serious		Nonserious	
		I	C	I	C
Addison's disease	1	1	1		
Adrenal disorder	4	2	2	2	2
Adrenal haemorrhage	3	3	3		
Adrenal insufficiency	8	8	8		
Adrenal mass	2			2	2
Adrenocortical insufficiency acute	16	16	16		
Adrenomegaly	4			4	4
Anovulatory cycle	10	6	6	4	4
Autoimmune hypothyroidism	2	2	2		
Autoimmune thyroid disorder	3	3	3		

* I=Interval, C=Cumulative
* AE=Adverse Event
* Multiple adverse events coding to the same Preferred Term may have been reported in some cases. Counts are provided for the number of unique Preferred Terms reported.

System Organ Class

Endocrine disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous			
		Serious		Nonserious	
		I	C	I	C
Autoimmune thyroiditis	30	30	30		
Basedow's disease	23	22	22	1	1
Diabetes insipidus	3	3	3		
Endocrine disorder	1			1	1
Goitre	41	19	19	22	22
Growth hormone deficiency	1	1	1		
Haemorrhagic thyroid cyst	1			1	1
Hyperaldosteronism	1	1	1		
Hypercalcaemia of malignancy	1			1	1
Hyperparathyroidism	2	1	1	1	1
Hyperparathyroidism primary	1			1	1
Hyperthyroidism	60	57	57	3	3
Hypoparathyroidism	1	1	1		
Hypopituitarism	2			2	2
Hypothyroidism	56	53	53	3	3
Inappropriate antidiuretic hormone secretion	1	1	1		
Myxoedema	1	1	1		
Ovulation delayed	2			2	2
Pituitary apoplexy	1	1	1		
Pituitary-dependent Cushing's syndrome	1	1	1		
Polyglandular autoimmune syndrome type I	1			1	1
Premature menarche	6			6	6
Primary hyperaldosteronism	2	1	1	1	1
Primary hyperthyroidism	1	1	1		
Secondary adrenocortical insufficiency	1	1	1		
Silent thyroiditis	1	1	1		
Thyroid cyst	1	1	1		

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* AE=Adverse Event
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System Organ Class

Endocrine disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous			
		Serious		Nonserious	
		I	C	I	C
Thyroid disorder	28	5	5	23	23
Thyroiditis	18	10	10	8	8
Thyroiditis acute	11	11	11		
Thyroiditis subacute	15	3	3	12	12
Thyroid mass	16	6	6	10	10
Thyroid pain	16	4	4	12	12
Thyrotoxic crisis	6	5	5	1	1
Total:	406	282	282	124	124

System Organ Class

Eye disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Abnormal sensation in eye	59	17	17	42	42		
Accommodation disorder	17	3	3	14	14		
Acute macular outer retinopathy	3	3	3				
Age-related macular degeneration	5	5	5				
Altered visual depth perception	2			2	2		
Amaurosis	6	6	6				
Amaurosis fugax	19	18	18	1	1		
Amblyopia	3	1	1	2	2		
Angle closure glaucoma	6	6	6				
Anisometropia	1			1	1		
Anterior chamber cell	1	1	1				
Arteriosclerotic retinopathy	1	1	1				
Asthenopia	226	84	84	142	142		
Atopic keratoconjunctivitis	1	1	1				

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System Organ Class

Eye disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Autoimmune uveitis	1	1	1				
Binocular eye movement disorder	5	4	4	1	1		
Blepharitis	33	8	8	25	25		
Blepharochalasis	1			1	1		
Blepharospasm	154	46	46	108	108		
Blindness	208	201	201	7	7	1	1
Blindness cortical	1	1	1				
Blindness transient	49	46	46	3	3		
Blindness unilateral	62	62	62				
Cataract	25	24	24	1	1		
Cataract nuclear	1	1	1				
Central vision loss	2	2	2				
Chalazion	5	3	3	2	2		
Charles Bonnet syndrome	1	1	1				
Chloropsia	2	2	2				
Chorioretinopathy	4	3	3	1	1		
Choroidal neovascularisation	4	4	4				
Choroiditis	1	1	1				
Chromatopsia	8	3	3	5	5		
Ciliary body disorder	1			1	1		
Ciliary muscle spasm	1			1	1		
Computer vision syndrome	1			1	1		
Conjunctival cyst	1			1	1		
Conjunctival disorder	5	2	2	3	3		
Conjunctival haemorrhage	147	142	142	5	5	3	3
Conjunctival hyperaemia	99	40	40	59	59		
Conjunctival irritation	14	3	3	11	11		

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System Organ Class

Eye disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Conjunctival oedema	14	4	4	10	10		
Conjunctival pallor	1	1	1				
Conjunctivitis allergic	11	2	2	9	9		
Corneal bleeding	2	2	2				
Corneal degeneration	1	1	1				
Corneal deposits	1			1	1		
Corneal disorder	3	2	2	1	1		
Corneal erosion	2	1	1	1	1		
Corneal infiltrates	1	1	1				
Corneal oedema	1			1	1		
Corneal opacity	5	5	5				
Corneal thinning	1	1	1				
Cyanopsia	2	2	2				
Cystoid macular oedema	2	2	2				
Dark circles under eyes	13	3	3	10	10		
Dermatochalasis	2			2	2		
Detachment of retinal pigment epithelium	1	1	1				
Diabetic eye disease	1			1	1		
Diplopia	371	214	214	157	157		
Dry age-related macular degeneration	1	1	1			1	1
Dry eye	251	63	63	187	188		
Dyschromatopsia	9	5	5	4	4		
Eczema eyelids	9			9	9		
Endocrine ophthalmopathy	8	8	8				
Episcleritis	21	11	11	10	10		
Erythema of eyelid	70	26	26	44	44		
Erythropsia	5	1	1	4	4		

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System Organ Class

Eye disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Excessive eye blinking	5	4	4	1	1		
Excessive ocular convergence	1	1	1				
Exophthalmos	11	11	11				
Exposure keratitis	1			1	1		
Extraocular muscle disorder	7	4	4	3	3		
Extraocular muscle paresis	9	9	9				
Eye allergy	18	5	5	13	13		
Eye colour change	11	4	4	7	7		
Eye discharge	73	16	16	57	57		
Eye disorder	241	69	69	172	172		
Eye haematoma	13	12	12	1	1		
Eye haemorrhage	148	144	144	4	4		
Eye infarction	3	3	3				
Eye inflammation	69	27	27	42	42		
Eye irritation	569	97	97	472	472	1	1
Eyelash changes	1			1	1		
Eyelid bleeding	2	2	2				
Eyelid cyst	3	1	1	2	2		
Eyelid disorder	30	8	8	22	22		
Eyelid exfoliation	4	2	2	2	2		
Eyelid function disorder	30	18	18	12	12		
Eyelid haematoma	14	3	3	11	11		
Eyelid irritation	30	9	9	21	21		
Eyelid margin crusting	6	1	1	5	5		
Eyelid myoclonus	4	3	3	1	1		
Eyelid myokymia	2	1	1	1	1		
Eyelid oedema	344	117	117	227	227	1	1

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System Organ Class

Eye disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Eyelid pain	57	14	14	43	43		
Eyelid ptosis	131	63	63	68	68		
Eyelid rash	22	10	10	12	12		
Eyelid retraction	1	1	1				
Eyelid sensory disorder	12	3	3	9	9		
Eyelid skin dryness	4	1	1	3	3		
Eyelids pruritus	55	22	22	33	33		
Eyelid thickening	3	1	1	2	2		
Eyelid vascular disorder	2			2	2		
Eye movement disorder	81	51	51	30	30		
Eye oedema	73	22	22	51	51		
Eye opacity	1			1	1		
Eye pain	1794	570	570	1223	1224	2	2
Eye paraesthesia	22	5	5	17	17		
Eye pruritus	555	159	159	395	396	2	2
Eye swelling	839	307	307	531	532	2	2
Eye symptom	9	4	4	5	5		
Eye ulcer	4	2	2	2	2		
Floppy eyelid syndrome	1	1	1				
Foreign body sensation in eyes	46	12	12	34	34		
Gaze palsy	19	19	19				
Giant papillary conjunctivitis	1	1	1				
Glare	10			10	10		
Glaucoma	23	23	23				
Halo vision	10	4	4	6	6		
Heterophoria	1	1	1				
Holmes-Adie pupil	1			1	1		

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System Organ Class

Eye disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Hyperaesthesia eye	4			4	4		
Hypermetropia	2	1	1	1	1		
Hypoaesthesia eye	36	14	14	22	22		
Idiopathic orbital inflammation	1	1	1				
Iridocyclitis	30	28	28	2	2		
Iritis	14	6	6	8	8		
Keratic precipitates	2	2	2				
Keratitis	12	7	7	5	5		
Keratoconus	1	1	1				
Lacrimal disorder	3	1	1	2	2		
Lacrimal structural disorder	1	1	1				
Lacrimation decreased	2	2	2				
Lacrimation disorder	2	1	1	1	1		
Lacrimation increased	504	132	132	372	372		
Lagophthalmos	10	5	5	5	5		
Lens disorder	1			1	1		
Lid margin discharge	1			1	1		
Lid sulcus deepened	2	1	1	1	1		
Limbal swelling	1	1	1				
Macular degeneration	11	11	11			1	1
Macular hole	3	3	3			1	1
Macular oedema	11	11	11			1	1
Macular rupture	2	2	2				
Maculopathy	7	5	6	1	1		
Meibomian gland dysfunction	3	1	1	2	2		
Metamorphopsia	26	15	16	10	10		
Miosis	17	6	6	11	11		

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System Organ Class

Eye disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Mydriasis	77	23	23	54	54		
Myopia	7	2	2	5	5		
Necrotising retinitis	2	2	2				
Neovascular age-related macular degeneration	2	2	2				
Night blindness	1			1	1		
Noninfective chorioretinitis	1	1	1				
Noninfective conjunctivitis	1			1	1		
Ocular discomfort	236	44	44	191	192		
Ocular dysmetria	1			1	1		
Ocular hyperaemia	631	172	172	459	459		
Ocular hypertension	3	3	3				
Ocular ischaemic syndrome	1	1	1				
Ocular myasthenia	6	6	6				
Ocular rosacea	1			1	1		
Ocular sarcoidosis	1	1	1				
Ocular vascular disorder	17	13	13	4	4		
Ocular vasculitis	1			1	1		
Oculogyric crisis	3	3	3			1	1
Open angle glaucoma	3	3	3				
Ophthalmic artery thrombosis	5	5	5				
Ophthalmic vein thrombosis	18	18	18				
Ophthalmoplegia	10	10	10				
Optic atrophy	2	2	2				
Optic disc haemorrhage	3	3	3				
Optic ischaemic neuropathy	15	15	15				
Optic nerve disorder	4	3	3	1	1	1	1
Optic nerve infarction	1	1	1				

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System Organ Class

Eye disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Optic neuropathy	4	4	4				
Orbital haematoma	3	3	3				
Orbital oedema	7	7	7				
Orbital swelling	1	1	1				
Oscillopsia	4			4	4		
Panophthalmitis	1	1	1				
Papilloedema	17	17	17				
Parophthalmia	2	2	2				
Periorbital discomfort	8	2	2	5	6		
Periorbital disorder	4			4	4		
Periorbital inflammation	1	1	1				
Periorbital oedema	83	27	27	56	56		
Periorbital pain	14	6	6	8	8		
Periorbital swelling	257	94	95	162	162		
Photophobia	780	258	258	521	522		
Photopsia	233	96	96	137	137		
Pigmentary glaucoma	1	1	1				
Punctate keratitis	1	1	1				
Pupil fixed	9	9	9				
Pupillary deformity	1	1	1				
Pupillary disorder	6	1	1	5	5		
Pupillary reflex impaired	5	4	4	1	1		
Pupils unequal	19	11	11	8	8		
Refraction disorder	1	1	1				
Retinal aneurysm	2	2	2				
Retinal artery embolism	3	3	3				
Retinal artery occlusion	50	50	50				

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System Organ Class

Eye disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Retinal artery thrombosis	9	8	8	1	1		
Retinal degeneration	1	1	1				
Retinal detachment	20	20	20				
Retinal disorder	5	3	3	2	2		
Retinal drusen	1	1	1				
Retinal exudates	4	4	4				
Retinal fovea disorder	2	2	2				
Retinal haemorrhage	21	21	21				
Retinal infarction	1	1	1				
Retinal ischaemia	2	2	2				
Retinal oedema	2	2	2				
Retinal pigment epitheliopathy	1	1	1				
Retinal tear	14	14	14				
Retinal toxicity	2	2	2				
Retinal vascular occlusion	7	7	7				
Retinal vascular thrombosis	15	13	13	2	2	1	1
Retinal vasculitis	2	2	2				
Retinal vein occlusion	72	71	71	1	1		
Retinal vein thrombosis	31	28	28	3	3	1	1
Retinopathy	2	2	2				
Retinopathy hypertensive	1	1	1				
Scintillating scotoma	14	2	2	12	12		
Scleral discolouration	12	4	4	8	8		
Scleral disorder	3	1	1	2	2		
Scleral haemorrhage	2	2	2				
Scleral hyperaemia	2			2	2		
Scleritis	14	14	14				

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System Organ Class

Eye disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Strabismus	25	14	14	11	11		
Subretinal haematoma	1	1	1				
Sudden visual loss	11	11	11				
Swelling of eyelid	348	122	122	225	226		
Ulcerative keratitis	6	6	6				
Uveitis	67	65	65	2	2	1	1
Vision blurred	2011	731	731	1278	1280	2	2
Visual acuity reduced	69	39	39	30	30	1	1
Visual acuity reduced transiently	3	1	1	2	2		
Visual brightness	4	3	3	1	1		
Visual field defect	112	55	55	57	57	1	1
Visual impairment	1044	459	460	584	584	3	3
Visual snow syndrome	3	3	3				
Vitreoretinal traction syndrome	2	2	2				
Vitreous degeneration	2	2	2				
Vitreous detachment	50	48	48	2	2	1	1
Vitreous disorder	5	4	4	1	1		
Vitreous floaters	113	48	48	65	65		
Vitreous haemorrhage	13	12	12	1	1		
Vitreous haze	1	1	1				
Vitreous opacities	1			1	1		
Vitritis	1	1	1				
Vogt-Koyanagi-Harada disease	1	1	1				
Xanthopsia	3	2	2	1	1		
Xerophthalmia	4	4	4				
Total:	14862	6028	6032	8820	8830	29	29

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System Organ Class

Gastrointestinal disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Abdominal adhesions	2	2	2				
Abdominal discomfort	1535	350	350	1182	1185	4	4
Abdominal distension	580	200	200	380	380	1	1
Abdominal hernia	2	1	1	1	1		
Abdominal mass	7	2	2	5	5		
Abdominal migraine	3	1	1	2	2		
Abdominal pain	5004	1135	1136	3865	3868	10	10
Abdominal pain lower	249	97	97	152	152		
Abdominal pain upper	3304	1110	1112	2190	2192	10	10
Abdominal rigidity	34	12	12	22	22		
Abdominal symptom	15	8	8	7	7		
Abdominal tenderness	25	11	11	14	14		
Abdominal wall haematoma	3	3	3				
Abdominal wall haemorrhage	3	3	3				
Abdominal wall oedema	1			1	1		
Abnormal faeces	151	12	12	139	139		
Acetonaemic vomiting	3			3	3		
Achlorhydria	1			1	1		
Acquired macroglossia	1	1	1				
Acute abdomen	13	13	13				
Acute haemorrhagic ulcerative colitis	1	1	1				
Aerophagia	9	3	3	6	6		
Allergic gastroenteritis	1	1	1				
Anaesthesia oral	39	7	7	32	32		
Anal erythema	1	1	1				
Anal fissure	2	1	1	1	1		
Anal haemorrhage	22	11	11	11	11		

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System Organ Class

Gastrointestinal disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Anal hypoaesthesia	1	1	1				
Anal incontinence	76	39	39	37	37	1	1
Anal inflammation	1			1	1		
Anal pruritus	6	1	1	5	5		
Anal rash	1			1	1		
Anal skin tags	1			1	1		
Anal spasm	1			1	1		
Anal sphincter atony	9	7	7	2	2		
Anal sphincter hypertonia	1			1	1		
Angina bullosa haemorrhagica	2	2	2				
Angular cheilitis	7	1	1	6	6		
Anorectal discomfort	10	1	1	9	9		
Anorectal disorder	1	1	1				
Anorectal swelling	1	1	1				
Aphthous ulcer	226	44	44	182	182	1	1
Apical granuloma	1			1	1		
Appendix disorder	1	1	1				
Aptyalism	15	4	4	11	11		
Ascites	10	9	9	1	1		
Atrophic glossitis	3	1	1	2	2		
Autoimmune pancreatitis	3	3	3				
Barrett's oesophagus	1	1	1				
Bile acid malabsorption	2			2	2		
Bowel movement irregularity	59	7	7	52	52		
Breath odour	26	10	10	16	16		
Burning mouth syndrome	10	3	3	7	7		
Cardiospasm	6	2	2	4	4		

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System Organ Class

Gastrointestinal disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Change of bowel habit	11	2	2	9	9		
Chapped lips	33	6	6	27	27		
Cheilitis	63	16	16	47	47		
Chronic gastritis	5	3	3	2	2		
Coating in mouth	5	2	2	3	3		
Coeliac artery stenosis	2	2	2				
Coeliac disease	10	10	10				
Colitis	80	42	42	38	38		
Colitis ischaemic	21	20	20	1	1		
Colitis microscopic	9	9	9				
Colitis ulcerative	92	86	86	6	6	3	3
Constipation	399	130	130	269	269		
Crohn's disease	52	49	49	3	3	3	3
Cyclic vomiting syndrome	1	1	1				
Defaecation disorder	3	2	2	1	1		
Defaecation urgency	35	11	11	24	24		
Dental caries	6	1	1	5	5		
Dental discomfort	20	2	2	18	18		
Dental dysaesthesia	1	1	1				
Dental paraesthesia	13	4	4	9	9		
Diabetic gastroenteropathy	1			1	1		
Diarrhoea	13157	3063	3065	10082	10092	28	28
Diarrhoea haemorrhagic	69	64	65	4	4		
Diarrhoea neonatal	1	1	1				
Discoloured vomit	10	4	4	6	6		
Diverticular perforation	1	1	1				
Diverticulum	9	5	5	4	4		

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System Organ Class

Gastrointestinal disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Diverticulum intestinal	10	6	6	4	4		
Diverticulum intestinal haemorrhagic	2	2	2				
Dry mouth	1153	308	310	838	843	3	3
Dumping syndrome	1			1	1		
Duodenal ulcer	3	3	3				
Duodenal ulcer haemorrhage	4	4	4				
Duodenal ulcer perforation	1	1	1				
Duodenitis	2	1	1	1	1		
Duodenogastric reflux	7	1	1	6	6		
Dysbiosis	2	2	2				
Dyschezia	16	6	6	10	10		
Dyspepsia	648	156	156	490	492	1	1
Dysphagia	1317	580	580	736	737	7	7
Enlarged uvula	41	22	22	19	19		
Enteritis	21	11	11	10	10	1	1
Enterocolitis	10	9	9	1	1		
Enterocolitis haemorrhagic	3	3	3				
Enterovesical fistula	2	2	2				
Eosinophilic colitis	1	1	1				
Eosinophilic oesophagitis	3	1	1	2	2		
Epigastric discomfort	38	16	16	22	22		
Epiploic appendagitis	1	1	1				
Erosive oesophagitis	1	1	1				
Eructation	115	33	33	82	82		
Faecaloma	10	10	10				
Faecal vomiting	5	5	5				
Faeces discoloured	101	28	28	73	73		

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System Organ Class

Gastrointestinal disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Faeces hard	10	2	2	8	8		
Faeces pale	15	9	9	6	6		
Faeces soft	68	17	17	51	51		
Flatulence	327	100	100	226	227	1	1
Food poisoning	17	5	5	12	12		
Frequent bowel movements	71	23	23	48	48		
Functional gastrointestinal disorder	31	14	14	17	17		
Gastric antral vascular ectasia	6	6	6				
Gastric dilatation	10	6	6	4	4		
Gastric disorder	90	20	20	70	70	1	1
Gastric haemorrhage	16	16	16				
Gastric ulcer	21	21	21				
Gastric ulcer haemorrhage	4	4	4				
Gastric varices haemorrhage	2	2	2				
Gastric volvulus	1	1	1				
Gastritis	93	33	33	60	60		
Gastritis erosive	4	4	4				
Gastrointestinal disorder	386	67	67	318	319	1	1
Gastrointestinal haemorrhage	70	69	69	1	1		
Gastrointestinal hypermotility	11	6	6	5	5		
Gastrointestinal hypomotility	6	4	4	2	2		
Gastrointestinal inflammation	15	6	6	9	9		
Gastrointestinal motility disorder	22	4	4	18	18		
Gastrointestinal mucosal disorder	1	1	1				
Gastrointestinal necrosis	12	12	12				
Gastrointestinal obstruction	2	2	2				
Gastrointestinal oedema	5	5	5				

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System Organ Class

Gastrointestinal disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Gastrointestinal pain	244	87	87	157	157	1	1
Gastrointestinal sounds abnormal	42	15	15	27	27		
Gastrointestinal tract irritation	4			4	4		
Gastrointestinal ulcer	1	1	1				
Gastrointestinal wall thickening	2			2	2		
Gastrooesophageal reflux disease	222	73	73	149	149	1	1
Gingival bleeding	106	45	45	60	61		
Gingival blister	17	5	5	12	12		
Gingival discolouration	4	3	3	1	1		
Gingival discomfort	17	4	4	13	13	1	1
Gingival disorder	19	3	3	16	16		
Gingival erythema	12	4	4	8	8		
Gingival hypertrophy	2	1	1	1	1		
Gingival oedema	4	1	1	3	3		
Gingival pain	135	54	54	81	81		
Gingival pruritus	1	1	1				
Gingival recession	3			3	3		
Gingival swelling	75	23	23	52	52		
Gingival ulceration	3			3	3		
Gingivitis ulcerative	3	3	3				
Glossitis	69	17	17	52	52		
Glossodynia	304	87	87	216	217		
Haematemesis	94	92	93	1	1	2	2
Haematochezia	221	217	217	4	4	1	1
Haemoperitoneum	2	2	2				
Haemorrhoidal haemorrhage	6	2	2	4	4		
Haemorrhoids	41	20	20	21	21		

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System Organ Class

Gastrointestinal disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Haemorrhoids thrombosed	7	5	5	2	2		
Hiatus hernia	22	10	10	12	12		
Hyperaesthesia teeth	44	10	10	34	34		
Hyperchlorhydria	17	9	9	8	8		
Hypertrophy of tongue papillae	8	1	1	7	7		
Hypoaesthesia oral	1422	430	430	989	992		
Hypoaesthesia teeth	10	2	2	8	8		
Ileal perforation	1	1	1				
Ileus	14	14	14				
Ileus paralytic	12	12	12				
Impaired gastric emptying	17	17	17				
Infantile vomiting	7	3	3	4	4		
Inflammatory bowel disease	9	9	9				
Infrequent bowel movements	4	1	1	3	3		
Inguinal hernia	2	2	2				
Internal hernia	1	1	1				
Intestinal angina	1	1	1				
Intestinal angioedema	2	1	1	1	1		
Intestinal atony	1			1	1		
Intestinal congestion	1			1	1		
Intestinal dilatation	1	1	1				
Intestinal haemorrhage	18	18	18			1	1
Intestinal infarction	8	8	8				
Intestinal ischaemia	42	42	42				
Intestinal mass	1	1	1				
Intestinal obstruction	28	28	28				
Intestinal perforation	4	4	4				

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System Organ Class

Gastrointestinal disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Intestinal polyp	1			1	1		
Intestinal pseudo-obstruction	2	2	2				
Intestinal ulcer	1	1	1				
Intra-abdominal haematoma	3	3	3				
Intra-abdominal haemorrhage	2	2	2				
Intussusception	14	13	13	1	1		
Irritable bowel syndrome	89	46	46	43	43		
Large intestinal haemorrhage	1	1	1				
Large intestinal obstruction	2	2	2				
Large intestine perforation	5	5	5				
Large intestine polyp	1			1	1		
Lip blister	66	23	23	43	43		
Lip discolouration	17	7	7	10	10		
Lip disorder	43	10	10	33	33		
Lip dry	79	27	27	52	52		
Lip erosion	1	1	1				
Lip erythema	34	10	10	24	24		
Lip exfoliation	13	4	4	9	9		
Lip haematoma	1	1	1				
Lip haemorrhage	8	3	3	5	5		
Lip oedema	358	135	135	223	223	2	2
Lip pain	118	33	33	85	85		
Lip pruritus	118	41	41	77	77		
Lip scab	1	1	1				
Lip swelling	1313	524	525	787	788	2	2
Lip ulceration	10	5	5	5	5		
Loose tooth	3	2	2	1	1		

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System Organ Class

Gastrointestinal disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Lower gastrointestinal haemorrhage	2	2	2				
Malabsorption	2	2	2				
Mallory-Weiss syndrome	3	3	3				
Malocclusion	1	1	1				
Megacolon	1	1	1				
Melaena	46	46	46				
Mesenteric arterial occlusion	3	3	3				
Mesenteric artery aneurysm	1	1	1				
Mesenteric artery embolism	3	3	3				
Mesenteric artery stenosis	2	2	2				
Mesenteric artery thrombosis	7	7	7				
Mesenteric panniculitis	2	2	2				
Mesenteric vascular insufficiency	1	1	1				
Mesenteric vascular occlusion	1	1	1				
Mesenteric vein thrombosis	27	27	27				
Mouth cyst	5	1	1	4	4		
Mouth haemorrhage	52	24	24	28	28		
Mouth swelling	229	99	99	129	130		
Mouth ulceration	307	121	121	185	186	2	2
Mucous stools	19	6	6	13	13		
Nausea	37653	8390	8402	29225	29251	92	92
Necrotising colitis	1	1	1				
Noninfective gingivitis	34	12	12	22	22		
Noninfective sialoadenitis	8	2	2	6	6		
Obstruction gastric	1	1	1				
Obstructive pancreatitis	4	4	4				
Obturator hernia	1	1	1				

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System Organ Class

Gastrointestinal disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Odynophagia	672	113	113	559	559	2	2
Oedema mouth	46	24	24	22	22	1	1
Oedematous pancreatitis	4	4	4				
Oesophageal achalasia	2	1	1	1	1		
Oesophageal discomfort	3	2	2	1	1		
Oesophageal disorder	5	4	4	1	1		
Oesophageal haemorrhage	1	1	1				
Oesophageal irritation	3	1	1	2	2		
Oesophageal oedema	2	2	2				
Oesophageal pain	18	7	7	11	11		
Oesophageal perforation	1	1	1				
Oesophageal spasm	13	5	5	8	8		
Oesophageal stenosis	3	3	3				
Oesophageal ulcer	1			1	1		
Oesophageal ulcer haemorrhage	1	1	1				
Oesophageal varices haemorrhage	2	2	2				
Oesophagitis	10	2	2	8	8		
Oral blood blister	17	6	6	11	11		
Oral discharge	2			2	2		
Oral discomfort	309	75	76	233	233	1	1
Oral disorder	76	21	21	55	55		
Oral dysaesthesia	29	7	7	22	22		
Oral hyperaesthesia	2	1	1	1	1		
Oral lichen planus	5	2	2	3	3		
Oral mucosa erosion	5			5	5		
Oral mucosa haematoma	2	1	1	1	1		
Oral mucosal blistering	97	19	19	78	78		

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System Organ Class

Gastrointestinal disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Oral mucosal discolouration	3	1	1	2	2		
Oral mucosal eruption	33	6	6	27	27		
Oral mucosal erythema	34	9	9	25	25		
Oral mucosal exfoliation	13	5	5	8	8		
Oral mucosal hypertrophy	1			1	1		
Oral mucosal roughening	6	2	2	4	4		
Oral pain	269	76	76	192	193		
Oral papule	1	1	1				
Oral pigmentation	1			1	1		
Oral pruritus	175	72	72	103	103		
Oral purpura	1	1	1				
Overflow diarrhoea	1			1	1		
Palatal disorder	10	3	3	7	7		
Palatal oedema	72	42	42	30	30		
Palatal swelling	44	21	21	23	23		
Palatal ulcer	2	1	1	1	1		
Pancreatic cyst	3	1	1	2	2		
Pancreatic disorder	5	4	4	1	1		
Pancreatic failure	2	1	1	1	1		
Pancreatic infarction	1	1	1				
Pancreatic steatosis	1			1	1		
Pancreatitis	54	53	53	1	1		
Pancreatitis acute	64	64	64				
Pancreatitis chronic	2	2	2				
Pancreatitis haemorrhagic	1	1	1				
Pancreatitis necrotising	3	3	3				
Pancreatitis relapsing	2	2	2				

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System Organ Class

Gastrointestinal disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Paraesthesia oral	2664	757	761	1896	1903	6	6
Parotid duct obstruction	1	1	1				
Parotid gland enlargement	27	7	7	20	20		
Pelvic floor dysfunction	1	1	1				
Peptic ulcer	3	3	3				
Peptic ulcer haemorrhage	6	6	6				
Peristalsis visible	1			1	1		
Pigmentation lip	1			1	1		
Plicated tongue	9	2	2	7	7		
Pneumoperitoneum	1	1	1				
Poor dental condition	1			1	1		
Pouchitis	1	1	1				
Proctalgia	16	6	6	10	10		
Proctitis	5	1	1	4	4		
Proctitis haemorrhagic	1	1	1				
Proctitis ulcerative	2	2	2				
Pylorospasm	1			1	1		
Rectal discharge	7	4	4	3	3		
Rectal haemorrhage	133	133	133				
Rectal polyp	2	1	1	1	1		
Rectal prolapse	1	1	1				
Rectal spasm	1			1	1		
Rectal tenesmus	7	2	2	5	5		
Rectal ulcer	1	1	1				
Reflux gastritis	19	2	2	17	17		
Regurgitation	11	3	3	8	8		
Retching	376	102	102	273	274	2	2

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System Organ Class

Gastrointestinal disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Retroperitoneal haemorrhage	2	2	2				
Saliva altered	2			2	2		
Saliva discolouration	3	1	1	2	2		
Salivary duct obstruction	1	1	1				
Salivary gland calculus	2			2	2		
Salivary gland disorder	7	3	3	4	4		
Salivary gland enlargement	23	8	8	15	15		
Salivary gland mass	1	1	1				
Salivary gland pain	36	9	9	27	27		
Salivary hypersecretion	159	46	46	113	113		
Scalloped tongue	5	2	2	3	3		
Small intestinal haemorrhage	8	8	8				
Small intestinal obstruction	7	7	7				
Splenic artery aneurysm	1	1	1				
Steatorrhoea	5	4	4	1	1		
Stiff tongue	13	9	9	4	4		
Stomach mass	1	1	1				
Stomatitis	209	55	55	154	154	1	1
Strawberry tongue	2	1	1	1	1		
Subileus	5	4	4	1	1		
Submaxillary gland enlargement	7	1	1	6	6		
Swollen tongue	1147	532	536	608	611	1	1
Teeth brittle	1			1	1		
Teething	16	3	3	13	13		
Terminal ileitis	1	1	1				
Thrombosis mesenteric vessel	5	5	5				
Tongue blistering	45	11	11	34	34		

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System Organ Class

Gastrointestinal disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Tongue coated	32	11	11	21	21	1	1
Tongue cyst	2	2	2				
Tongue discolouration	62	16	16	46	46		
Tongue discomfort	188	51	51	137	137		
Tongue disorder	163	57	57	106	106		
Tongue dry	48	16	16	32	32		
Tongue eruption	22	9	9	13	13		
Tongue erythema	37	8	8	29	29		
Tongue exfoliation	6	1	1	5	5		
Tongue geographic	3			3	3		
Tongue haematoma	5	1	1	4	4		
Tongue haemorrhage	5			5	5		
Tongue induration	1			1	1		
Tongue movement disturbance	19	13	13	6	6		
Tongue oedema	217	129	129	88	88	2	2
Tongue pruritus	125	40	41	84	84		
Tongue rough	7	1	1	6	6		
Tongue spasm	13	5	5	8	8		
Tongue ulceration	54	19	19	35	35		
Toothache	323	74	74	248	249		
Tooth discolouration	2	1	1	1	1		
Tooth disorder	54	2	2	52	52		
Tooth erosion	1			1	1		
Tooth impacted	1			1	1		
Tooth loss	6	3	3	3	3		
Trichoglossia	12	3	3	9	9		
Truncus coeliacus thrombosis	2	2	2				

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System Organ Class

Gastrointestinal disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Upper gastrointestinal haemorrhage	13	13	13				
Uvulitis	8	5	5	3	3		
Varices oesophageal	2	1	1	1	1		
Visceral venous thrombosis	3	3	3				
Visceroptosis	1			1	1		
Volvulus	4	4	4				
Volvulus of small bowel	1	1	1				
Vomiting	11395	3457	3458	7931	7937	30	30
Vomiting projectile	84	38	38	46	46		
Total:	94581	25808	25841	68659	68740	228	228

System Organ Class

General disorders and administration site conditions

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Abscess sterile	1			1	1		
Acute phase reaction	2	1	1	1	1		
Adhesion	1	1	1				
Administration site bruise	13			13	13		
Administration site discomfort	2			2	2		
Administration site erythema	16			16	16		
Administration site extravasation	1			1	1		
Administration site haematoma	3			3	3		
Administration site hypersensitivity	1			1	1		
Administration site hypoaesthesia	1			1	1		
Administration site induration	4			4	4		
Administration site inflammation	5			5	5		

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System Organ Class

General disorders and administration site conditions

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Administration site irritation	3			3	3		
Administration site joint discomfort	1			1	1		
Administration site joint erythema	2			2	2		
Administration site joint movement impairment	3	2	2	1	1		
Administration site joint pain	4			4	4		
Administration site joint warmth	1			1	1		
Administration site lymphadenopathy	8			8	8		
Administration site movement impairment	6	1	1	5	5		
Administration site nodule	1			1	1		
Administration site oedema	34			34	34		
Administration site pain	724	4	4	720	720		
Administration site paraesthesia	3			3	3		
Administration site pruritus	10			10	10		
Administration site rash	1			1	1		
Administration site reaction	38	1	1	37	37		
Administration site swelling	25			25	25		
Administration site warmth	5			5	5		
Adverse drug reaction	98	35	35	63	63		
Adverse event	88	4	4	84	84	1	1
Adverse food reaction	1			1	1		
Adverse reaction	22	3	3	19	19	1	1
Alcohol interaction	5	4	4	1	1		
Apparent death	1	1	1				
Application site acne	4	1	1	3	3		
Application site bruise	3			3	3		
Application site burn	1			1	1		
Application site coldness	4	1	1	3	3		

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System Organ Class

General disorders and administration site conditions

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Application site dermatitis	1			1	1		
Application site discomfort	1			1	1		
Application site erythema	98	1	1	97	97		
Application site haematoma	1			1	1		
Application site haemorrhage	4	1	1	3	3		
Application site hyperaesthesia	1			1	1		
Application site hypoaesthesia	5			5	5		
Application site induration	5			5	5		
Application site inflammation	2			2	2		
Application site irritation	1	1	1				
Application site joint pain	3			3	3		
Application site joint swelling	4			4	4		
Application site lymphadenopathy	7			7	7		
Application site movement impairment	3			3	3		
Application site nerve damage	1			1	1		
Application site oedema	8			8	8		
Application site pain	961	1	1	960	960		
Application site papules	2			2	2		
Application site paraesthesia	1			1	1		
Application site plaque	1			1	1		
Application site pruritus	33			33	33		
Application site rash	2			2	2		
Application site reaction	75			75	75		
Application site swelling	180			180	180		
Application site vesicles	4	2	2	2	2		
Application site warmth	5			5	5		
Asthenia	24363	3580	3582	20770	20781	31	31

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System Organ Class

General disorders and administration site conditions

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Atrophy	2	1	1	1	1		
Axillary pain	3398	909	909	2487	2489	7	7
Brain death	10	10	10				
Breakthrough pain	3	1	1	2	2		
Calcinosis	1			1	1		
Capsular contracture associated with breast implant	2	1	1	1	1		
Capsular contracture associated with implant	1	1	1				
Cardiac death	20	20	20				
Catheter site haemorrhage	1			1	1		
Catheter site pain	2			2	2		
Challenge site reaction	4			4	4		
Chest discomfort	3338	1256	1259	2072	2079	5	5
Chest pain	5059	2254	2257	2798	2802	15	15
Chills	41169	6147	6151	34993	35018	71	71
Chronic disease	1			1	1		
Chronic fatigue syndrome	64	48	48	16	16	1	1
Complication associated with device	4	2	2	2	2		
Concomitant disease aggravated	27	16	16	11	11		
Concomitant disease progression	11	9	9	2	2		
Condition aggravated	1997	889	890	1106	1107	6	6
Crepitations	21	5	5	16	16		
Critical illness	1	1	1				
Crying	333	71	71	262	262	1	1
Cyst	38	9	9	29	29		
Cyst rupture	2			2	2		
Death	1259	1259	1259			1	1
Death neonatal	1	1	1				

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System Organ Class

General disorders and administration site conditions

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Decreased activity	18	6	6	12	12		
Decreased gait velocity	1			1	1		
Deformity	9	5	5	4	4		
Device embolisation	1	1	1				
Device related thrombosis	1	1	1				
Discharge	14	4	4	10	10		
Discomfort	1623	392	392	1231	1231	5	5
Disease complication	1	1	1				
Disease progression	30	22	22	8	8		
Disease recurrence	1028	766	766	259	262	4	4
Drowning	7	6	6	1	1		
Drug effective for unapproved indication	12			12	12		
Drug effect less than expected	1			1	1		
Drug ineffective	5187	5157	5162	25	25	28	28
Drug interaction	137	45	45	92	92	2	2
Drug intolerance	7	3	3	4	4		
Drug resistance	1	1	1				
Drug tolerance	1			1	1		
Drug withdrawal syndrome	4	2	2	2	2		
Effusion	10	6	6	4	4		
Enanthema	6	3	3	3	3		
Energy increased	54	5	5	49	49		
Exercise tolerance decreased	53	18	18	35	35	1	1
Extensive swelling of vaccinated limb	426	85	85	341	341		
Extravasation	4	3	3	1	1		
Eye complication associated with device	1	1	1				
Face oedema	514	231	231	283	283	2	2

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System Organ Class

General disorders and administration site conditions

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Facial discomfort	69	15	15	53	54		
Facial pain	471	180	180	291	291		
Fatigue	54480	11297	11303	43143	43177	205	205
Fat necrosis	2	1	1	1	1		
Fat tissue increased	3	1	1	2	2		
Feeling abnormal	5337	1457	1460	3869	3877	8	8
Feeling cold	3275	871	871	2403	2404	10	10
Feeling drunk	182	64	65	117	117		
Feeling hot	3934	1047	1049	2873	2885	2	2
Feeling jittery	118	26	27	91	91	1	1
Feeling of body temperature change	686	240	240	444	446		
Feeling of relaxation	10	3	3	7	7		
Fever neonatal	3	2	2	1	1		
Fibrosis	2	1	1	1	1		
Foaming at mouth	19	12	12	7	7		
Food interaction	1			1	1		
Foreign body reaction	2	1	1	1	1		
Gait deviation	2	1	1	1	1		
Gait disturbance	1712	678	678	1034	1034	2	2
Gait inability	465	250	250	215	215	1	1
Generalised oedema	32	16	16	16	16		
General physical health deterioration	695	459	459	236	236		
General symptom	12	3	3	9	9		
Glassy eyes	15	5	5	10	10		
Granuloma	4	1	1	3	3		
Gravitational oedema	5			5	5		
Haemorrhagic cyst	2	2	2				

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System Organ Class

General disorders and administration site conditions

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Hangover	112	40	40	71	72	1	1
Hernia	10	3	3	7	7		
Hernia pain	2			2	2		
High-pitched crying	1			1	1		
Hunger	61	7	7	54	54		
Hyperpyrexia	427	417	417	10	10	5	5
Hyperthermia	410	115	115	295	295		
Hypertrophy	2			2	2		
Hypothermia	181	175	175	6	6	1	1
Idiosyncratic drug reaction	3			3	3		
Ill-defined disorder	10	5	5	5	5		
Illness	2642	821	821	1819	1821	5	5
Immediate post-injection reaction	3	1	1	2	2		
Impaired healing	17	6	6	11	11		
Impaired self-care	5	3	3	2	2		
Implant site nodule	1			1	1		
Implant site pain	2	1	1	1	1		
Implant site swelling	2			2	2		
Inadequate analgesia	3	2	2	1	1		
Induration	1418	47	47	1371	1371		
Inflammation	2039	307	307	1732	1732		
Inflammatory pain	22	10	10	12	12		
Influenza like illness	8597	1758	1759	6834	6838	10	10
Infusion site erythema	2			2	2		
Infusion site haemorrhage	1	1	1				
Infusion site joint movement impairment	1			1	1		
Infusion site joint swelling	2			2	2		

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System Organ Class

General disorders and administration site conditions

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Infusion site lymphadenopathy	1			1	1		
Infusion site mobility decreased	3			3	3		
Infusion site pain	8			8	8		
Infusion site paraesthesia	1			1	1		
Infusion site rash	1			1	1		
Infusion site streaking	1			1	1		
Infusion site swelling	1			1	1		
Infusion site urticaria	1			1	1		
Infusion site warmth	1			1	1		
Inhibitory drug interaction	9	4	4	5	5		
Injected limb mobility decreased	375	55	55	320	320	1	1
Injection site bruising	51	2	2	49	49		
Injection site cyst	1			1	1		
Injection site discharge	2			2	2		
Injection site discolouration	19	2	2	17	17		
Injection site discomfort	76			76	76		
Injection site eczema	2			2	2		
Injection site erythema	1169	18	18	1151	1151		
Injection site exfoliation	1			1	1		
Injection site extravasation	18			17	18		
Injection site granuloma	1			1	1		
Injection site haematoma	50	1	1	49	49		
Injection site haemorrhage	36			36	36		
Injection site hyperaesthesia	2			2	2		
Injection site hypersensitivity	11	1	1	10	10		
Injection site hypoaesthesia	39	1	1	38	38		
Injection site indentation	5	1	1	4	4		

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System Organ Class

General disorders and administration site conditions

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Injection site induration	212			212	212		
Injection site inflammation	65	1	1	64	64		
Injection site injury	4			4	4		
Injection site irritation	9			9	9		
Injection site joint discomfort	1			1	1		
Injection site joint erythema	6			6	6		
Injection site joint movement impairment	16	1	1	15	15		
Injection site joint pain	49			49	49		
Injection site joint swelling	5			5	5		
Injection site joint warmth	2			2	2		
Injection site lymphadenopathy	18			18	18		
Injection site macule	2			2	2		
Injection site mass	157	10	10	147	147		
Injection site movement impairment	9	1	1	8	8		
Injection site muscle weakness	11	2	2	9	9		
Injection site nerve damage	1			1	1		
Injection site nodule	11			11	11		
Injection site oedema	579			579	579		
Injection site pain	10102	107	107	9995	9995	1	1
Injection site pallor	1			1	1		
Injection site papule	2			2	2		
Injection site paraesthesia	71			71	71		
Injection site pruritus	455	4	4	451	451		
Injection site rash	127	7	7	120	120		
Injection site reaction	463	13	13	450	450		
Injection site scab	3			3	3		
Injection site scar	3			3	3		

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System Organ Class

General disorders and administration site conditions

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Injection site swelling	622	9	9	613	613		
Injection site urticaria	103	2	2	101	101		
Injection site vesicles	6	1	1	5	5		
Injection site warmth	193	6	6	187	187		
Injury associated with device	10	1	1	9	9		
Instillation site pain	2			2	2		
Instillation site warmth	1			1	1		
Irritability postvaccinal	34	4	4	30	30		
Lithiasis	1			1	1		
Localised oedema	201	60	60	141	141	1	1
Local reaction	686	48	48	638	638		
Loss of control of legs	32	31	31	1	1		
Malaise	27705	5022	5025	22666	22680	82	82
Mass	213	46	46	167	167		
Medical device pain	2	1	1	1	1		
Medical device site pain	1			1	1		
Moaning	19	10	10	9	9		
Mucosal discolouration	3	1	1	2	2		
Mucosal disorder	16	5	5	11	11		
Mucosal dryness	25	6	6	19	19	1	1
Mucosal haemorrhage	9	7	7	2	2		
Mucosal hyperaemia	3	1	1	2	2		
Mucosal inflammation	9	3	3	6	6		
Mucosal pain	2			2	2		
Mucosal ulceration	2	2	2				
Mucosa vesicle	1	1	1				
Multimorbidity	2	2	2				

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System Organ Class

General disorders and administration site conditions

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Multi-organ disorder	8	6	6	2	2		
Multiple organ dysfunction syndrome	76	76	76			1	1
Necrosis	10	10	10				
No adverse event	94			93	94		
Nodule	1432	58	58	1374	1374		
Non-cardiac chest pain	26	8	8	18	18		
Non-pitting oedema	6	2	2	4	4		
Nonspecific reaction	6			6	6		
No reaction on previous exposure to drug	14	1	1	13	13		
Obstruction	8	4	4	4	4		
Oedema	1933	217	217	1716	1716	1	1
Oedema due to cardiac disease	1	1	1				
Oedema mucosal	19	13	13	6	6		
Oedema peripheral	783	295	295	488	488	7	7
Oral administration complication	2	1	1	1	1		
Organ failure	4	4	4				
Pain	25715	4570	4572	21112	21143	26	26
Papillitis	1			1	1		
Pelvic mass	2	2	2				
Perforation	3	3	3				
Performance status decreased	28	6	6	22	22		
Peripheral swelling	4579	1479	1479	3094	3100	7	7
Physical deconditioning	58	29	29	29	29		
Pneumatosis	1	1	1				
Polyp	4	1	1	3	3		
Polyserositis	3	3	3				
Potentiating drug interaction	99	1	1	98	98		

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System Organ Class

General disorders and administration site conditions

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Pre-existing condition improved	42	1	1	41	41		
Pre-existing disease	1			1	1		
Product intolerance	1	1	1				
Prolapse	1			1	1		
Prosthetic cardiac valve thrombosis	1	1	1				
Pseudoallergic reaction	2	1	1	1	1		
Puncture site bruise	9	2	2	7	7		
Puncture site discharge	1	1	1				
Puncture site erythema	5			5	5		
Puncture site haematoma	3	2	2	1	1		
Puncture site haemorrhage	1			1	1		
Puncture site induration	19			19	19		
Puncture site oedema	9			9	9		
Puncture site pain	74			74	74		
Puncture site pruritus	5			5	5		
Puncture site reaction	1			1	1		
Puncture site swelling	4			4	4		
Pyrexia	64149	10756	10762	53351	53387	129	129
Reactogenicity event	15	12	12	3	3		
Rebound effect	1	1	1				
Screaming	22	8	8	14	14		
Secretion discharge	77	15	15	62	62		
Sensation of blood flow	12	4	4	8	8		
Sensation of foreign body	421	190	190	231	231		
Sense of oppression	58	20	20	38	38	1	1
Sensitivity to weather change	11	3	3	7	8		
Serositis	2	2	2				

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System Organ Class

General disorders and administration site conditions

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Shoulder injury related to vaccine administration	27	17	17	10	10		
Sluggishness	132	25	25	106	107		
Soft tissue inflammation	2			2	2		
Stenosis	10	9	9	1	1		
Sudden cardiac death	29	29	29				
Sudden death	329	329	329			1	1
Sudden infant death syndrome	1	1	1				
Suprapubic pain	3	2	2	1	1		
Swelling	3742	1019	1019	2719	2723	3	3
Swelling face	2126	792	792	1332	1334	5	5
Symptom recurrence	14	5	5	9	9		
Systemic inflammatory response syndrome	32	32	32				
Temperature intolerance	51	19	19	32	32		
Temperature regulation disorder	279	31	31	248	248		
Tenderness	877	137	137	740	740	3	3
Terminal state	7	7	7				
Therapeutic product effect decreased	3			3	3		
Therapeutic product effect delayed	2	1	1	1	1		
Therapeutic product effect incomplete	1	1	1				
Therapeutic product effect increased	1	1	1				
Therapeutic product effect prolonged	3	1	1	2	2		
Therapeutic product ineffective	2	1	1	1	1		
Therapeutic response decreased	2	1	1	1	1		
Therapeutic response delayed	1			1	1		
Therapeutic response increased	1			1	1		
Therapeutic response unexpected	456	14	14	442	442		
Thirst	610	186	186	424	424	1	1

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System Organ Class

General disorders and administration site conditions

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Thirst decreased	8	2	2	6	6		
Tissue infiltration	1			1	1		
Treatment noncompliance	1	1	1				
Ulcer	32	12	12	20	20		
Ulcer haemorrhage	4	4	4				
Unevaluable event	7	1	1	6	6		
Vaccination failure	1598	1590	1590	8	8	22	22
Vaccination site abscess sterile	3	3	3				
Vaccination site anaesthesia	6	3	3	3	3		
Vaccination site atrophy	5	1	1	4	4		
Vaccination site bruising	471	102	102	369	369	1	1
Vaccination site calcification	1	1	1				
Vaccination site coldness	25	4	4	21	21		
Vaccination site cyst	4	1	1	3	3		
Vaccination site dermatitis	21	5	5	16	16		
Vaccination site discharge	13	2	2	11	11		
Vaccination site discolouration	119	21	21	98	98		
Vaccination site discomfort	599	63	63	534	536		
Vaccination site dryness	5	1	1	4	4		
Vaccination site dysaesthesia	15	4	4	11	11		
Vaccination site eczema	16	2	2	14	14		
Vaccination site erosion	2			2	2		
Vaccination site erythema	5858	769	769	5085	5089	2	2
Vaccination site exfoliation	5	1	1	4	4		
Vaccination site extravasation	29	2	2	27	27		
Vaccination site granuloma	5	1	1	4	4		
Vaccination site haematoma	699	43	43	656	656		

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* Multiple adverse events coding to the same Preferred Term may have been reported in some cases. Counts are provided for the number of unique Preferred Terms reported.

System Organ Class

General disorders and administration site conditions

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Vaccination site haemorrhage	219	49	49	170	170		
Vaccination site hyperaesthesia	59	16	16	43	43		
Vaccination site hypersensitivity	125	12	12	113	113		
Vaccination site hypertrophy	3	2	2	1	1		
Vaccination site hypoaesthesia	186	48	48	134	138		
Vaccination site induration	924	103	103	819	821		
Vaccination site inflammation	3202	104	104	3098	3098	2	2
Vaccination site injury	13	1	1	12	12		
Vaccination site irritation	59	9	9	50	50		
Vaccination site ischaemia	1	1	1				
Vaccination site joint discomfort	8	3	3	5	5		
Vaccination site joint erythema	145	9	9	136	136		
Vaccination site joint inflammation	17	4	4	13	13		
Vaccination site joint movement impairment	141	33	33	108	108		
Vaccination site joint pain	185	21	21	164	164		
Vaccination site joint swelling	109	4	4	105	105		
Vaccination site joint warmth	9	1	1	8	8		
Vaccination site lymphadenopathy	545	55	55	490	490		
Vaccination site macule	24			24	24		
Vaccination site mass	806	232	232	572	574	2	2
Vaccination site movement impairment	573	159	159	412	414		
Vaccination site necrosis	7	7	7				
Vaccination site nerve damage	7	2	2	5	5		
Vaccination site nodule	124	9	9	115	115		
Vaccination site oedema	1366	162	162	1204	1204	1	1
Vaccination site pain	36931	3812	3813	33059	33118	83	83
Vaccination site pallor	4	1	1	3	3		

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System Organ Class

General disorders and administration site conditions

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Vaccination site papule	27	4	4	23	23		
Vaccination site paraesthesia	327	55	56	271	271		
Vaccination site phlebitis	3	1	1	2	2		
Vaccination site photosensitivity reaction	1			1	1		
Vaccination site plaque	10	1	1	9	9		
Vaccination site pruritus	2322	305	305	2016	2017	1	1
Vaccination site rash	686	148	148	538	538		
Vaccination site reaction	2610	495	495	2114	2115	2	2
Vaccination site recall reaction	1			1	1		
Vaccination site scab	12	3	3	9	9		
Vaccination site scar	13	2	2	11	11		
Vaccination site streaking	1			1	1		
Vaccination site swelling	6294	786	786	5501	5508	16	16
Vaccination site thrombosis	4	4	4				
Vaccination site ulcer	3	2	2	1	1		
Vaccination site urticaria	228	49	49	177	179		
Vaccination site vasculitis	1			1	1		
Vaccination site vesicles	70	17	17	53	53		
Vaccination site warmth	3477	336	336	3139	3141	2	2
Vascular stent stenosis	1	1	1				
Vascular stent thrombosis	5	5	5				
Vessel puncture site bruise	1			1	1		
Vessel puncture site haematoma	1			1	1		
Vessel puncture site haemorrhage	1				1		
Vessel puncture site injury	1				1		
Vessel puncture site swelling	1			1	1		
Visceral pain	4			4	4		

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System Organ Class

General disorders and administration site conditions

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Withdrawal syndrome	11	5	5	6	6		
Xerosis	2	1	1	1	1		
Total:	404591	79360	79405	324881	325186	838	838

System Organ Class

Hepatobiliary disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Acute hepatic failure	5	5	5				
Autoimmune hepatitis	14	14	14				
Bile duct stone	3	3	3				
Biliary colic	21	11	11	10	10		
Biliary cyst	1			1	1		
Biliary dilatation	5	5	5				
Biliary tract disorder	4	3	3	1	1		
Cholangitis	5	5	5				
Cholangitis acute	1	1	1				
Cholangitis sclerosing	3	3	3				
Cholecystitis	17	17	17				
Cholecystitis acute	4	4	4				
Cholelithiasis	26	19	19	7	7		
Cholestasis	26	25	25	1	1		
Cholestatic liver injury	3	3	3				
Congestive hepatopathy	4	4	4				
Deficiency of bile secretion	1	1	1				
Drug-induced liver injury	7	7	7				
Gallbladder disorder	17	9	9	8	8	1	1

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System Organ Class

Hepatobiliary disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Gallbladder enlargement	3	3	3				
Gallbladder oedema	2	2	2				
Gallbladder polyp	1			1	1		
Granulomatous liver disease	2	2	2				
Hepatic artery embolism	1	1	1				
Hepatic cirrhosis	6	6	6				
Hepatic cyst	11	3	3	8	8		
Hepatic cytolysis	31	30	30	1	1		
Hepatic failure	19	19	19				
Hepatic function abnormal	60	31	31	29	29		
Hepatic haematoma	1	1	1				
Hepatic haemorrhage	5	5	5				
Hepatic infarction	5	5	5				
Hepatic lesion	5	4	4	1	1		
Hepatic mass	2			2	2		
Hepatic necrosis	1	1	1				
Hepatic pain	47	17	17	30	30		
Hepatic steatosis	18	6	6	12	12		
Hepatic vascular thrombosis	1	1	1				
Hepatic vein thrombosis	2	2	2				
Hepatitis	30	30	30				
Hepatitis acute	24	23	23	1	1		
Hepatitis cholestatic	9	9	9				
Hepatitis toxic	1	1	1				
Hepatobiliary disease	1			1	1		
Hepatocellular injury	6	6	6				
Hepatomegaly	15	11	11	4	4	1	1

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System Organ Class

Hepatobiliary disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Hepatorenal syndrome	1	1	1				
Hydrocholecystis	1	1	1				
Hyperbilirubinaemia	10	10	10				
Hypertransaminasaemia	8	5	5	3	3	1	1
Immune-mediated hepatic disorder	1	1	1				
Immune-mediated hepatitis	1	1	1				
Ischaemic hepatitis	1	1	1				
Jaundice	72	56	56	16	16		
Jaundice cholestatic	5	5	5				
Liver disorder	35	23	23	12	12		
Liver injury	22	20	20	2	2		
Liver tenderness	4	2	2	2	2		
Mixed liver injury	2	1	1	1	1		
Ocular icterus	9	1	1	8	8		
Periportal oedema	1	1	1				
Pneumobilia	1	1	1				
Portal hypertension	2	2	2				
Portal vein embolism	1	1	1				
Portal vein phlebitis	1	1	1				
Portal vein thrombosis	33	33	33				
Portosplenomesenteric venous thrombosis	3	3	3				
Primary biliary cholangitis	1	1	1				
Sphincter of Oddi dysfunction	1	1	1				
Total:	692	530	530	162	162	3	3

System Organ Class

Immune system disorders

Spontaneous		Non Interventional Study	

* I=Interval, C=Cumulative
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System Organ Class

Immune system disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Allergic oedema	29	17	17	12	12		
Allergic reaction to excipient	26	13	13	13	13		
Allergy to animal	3	1	1	2	2		
Allergy to arthropod bite	4	1	1	3	3		
Allergy to arthropod sting	6	2	2	4	4		
Allergy to chemicals	10	5	5	5	5		
Allergy to metals	1			1	1		
Allergy to plants	1			1	1		
Allergy to synthetic fabric	1			1	1		
Allergy to vaccine	360	159	161	196	199	2	2
Amyloidosis	3	3	3				
Amyloidosis senile	1	1	1				
Anamnestic reaction	4	2	2	2	2		
Anaphylactic reaction	3420	3376	3383	37	37	4	4
Anaphylactic shock	419	411	411	8	8	2	2
Anaphylactoid reaction	77	74	76	1	1		
Anaphylactoid shock	5	5	5				
Anti-neutrophil cytoplasmic antibody positive vasculitis	4	4	4				
Atopy	5	2	2	3	3		
Autoimmune disorder	87	83	83	4	4		
Bacille Calmette-Guerin scar reactivation	27	6	6	21	21		
Cell-mediated immune deficiency	1	1	1				
Contrast media allergy	2	1	1	1	1		
Contrast media reaction	1	1	1				
Corneal graft rejection	8	8	8				
Cytokine release syndrome	1	1	1				
Cytokine storm	3	2	2	1	1		

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System Organ Class

Immune system disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Decreased immune responsiveness	15	4	4	11	11		
Drug hypersensitivity	193	74	74	118	119		
Eosinophilic granulomatosis with polyangiitis	1	1	1				
Food allergy	53	19	19	34	34		
Graft versus host disease	2	2	2				
Haemophagocytic lymphohistiocytosis	10	10	10				
Hashitoxicosis	1	1	1				
Hypersensitivity	3173	1437	1441	1731	1732	11	11
Hypogammaglobulinaemia	6	6	6				
Immune-mediated adverse reaction	13	9	9	4	4		
Immune reconstitution inflammatory syndrome	2	2	2				
Immune system disorder	131	50	50	81	81		
Immunisation reaction	16	6	6	10	10	1	1
Immunodeficiency	24	22	22	2	2	3	3
Immunodeficiency common variable	2	2	2				
Immunosuppression	4	2	2	2	2		
Kidney transplant rejection	1	1	1				
Lung transplant rejection	1	1	1				
Multiple allergies	11	5	5	6	6		
Multisystem inflammatory syndrome in children	1	1	1				
Mycotic allergy	1			1	1		
Oral allergy syndrome	4	2	2	2	2		
Perfume sensitivity	1			1	1		
Reaction to colouring	2	1	1	1	1		
Reaction to excipient	39	20	20	19	19		
Reaction to preservatives	7	3	3	4	4		
Renal transplant failure	1	1	1				

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System Organ Class

Immune system disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Rubber sensitivity	3	2	2	1	1		
Sarcoidosis	22	22	22				
Seasonal allergy	105	31	31	74	74		
Sensitisation	17	3	3	14	14		
Serum sickness	10	8	8	2	2		
Serum sickness-like reaction	5	3	3	2	2		
Solid organ transplant rejection	1	1	1				
Systemic immune activation	5	5	5				
Transplant rejection	1	1	1				
Type I hypersensitivity	77	76	76	1	1		
Type II hypersensitivity	4	4	4				
Type III immune complex mediated reaction	8	8	8				
Type IV hypersensitivity reaction	38	15	15	23	23		
Total:	8520	6040	6055	2460	2465	23	23

System Organ Class

Infections and infestations

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Abdominal abscess	2	2	2				
Abdominal infection	8	8	8				
Abdominal sepsis	2	2	2				
Abdominal wall abscess	1	1	1				
Abortion infected	1	1	1				
Abscess	68	22	22	46	46		
Abscess jaw	2	1	1	1	1		
Abscess limb	9	4	4	5	5		

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System Organ Class

Infections and infestations

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Abscess neck	2	1	1	1	1		
Abscess of eyelid	1	1	1				
Abscess of salivary gland	2	2	2				
Abscess oral	5	4	4	1	1		
Abscess rupture	1	1	1				
Abscess soft tissue	1			1	1		
Abscess sweat gland	1			1	1		
Acarodermatitis	8	6	6	2	2		
Acne pustular	4	2	2	2	2		
Acute endocarditis	1	1	1				
Acute haemorrhagic conjunctivitis	1			1	1		
Acute sinusitis	5	2	2	3	3		
Adenopathy syphilitic	4	4	4				
Adenoviral conjunctivitis	1			1	1		
Administration site abscess	1			1	1		
Aerococcus urinae infection	1	1	1				
African trypanosomiasis	2	2	2				
Amniotic cavity infection	1	1	1				
Anal abscess	4	4	4				
Anal candidiasis	2			2	2		
Anal infection	1			1	1		
Appendicitis	125	125	125			1	1
Appendicitis perforated	15	15	15				
Arthritis bacterial	3	3	3				
Arthritis infective	4	4	4				
Arthritis viral	2	1	1	1	1		
Arthropod infestation	1	1	1				

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System Organ Class

Infections and infestations

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Asymptomatic bacteriuria	3	2	2	1	1		
Asymptomatic COVID-19	562	511	511	51	51	5	5
Atypical pneumonia	14	13	13	1	1		
Babesiosis	2	1	1	1	1		
Bacteraemia	10	10	10				
Bacterial diarrhoea	1	1	1				
Bacterial disease carrier	2	1	1	1	1		
Bacterial infection	37	22	22	15	15		
Bacterial pyelonephritis	2	2	2				
Bacterial rhinitis	1	1	1				
Bacterial sepsis	7	7	7				
Bacterial vaginosis	3			3	3		
Bacteriuria	4	2	2	2	2		
Bartholinitis	2	1	1	1	1		
Beta haemolytic streptococcal infection	4	4	4				
Biliary sepsis	2	2	2				
Blastocystis infection	1	1	1				
Blister infected	5			5	5		
Body tinea	2			2	2		
Bone abscess	1	1	1				
Borrelia infection	5	5	5				
Breast abscess	7	6	6	1	1		
Breast cellulitis	2	2	2				
Bronchiolitis	4	4	4				
Bronchitis	151	57	58	92	93	1	1
Bronchitis bacterial	5	5	5				
Bronchopulmonary aspergillosis	1	1	1				

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System Organ Class

Infections and infestations

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Bursitis infective	1	1	1				
Campylobacter gastroenteritis	2	2	2				
Campylobacter infection	1	1	1				
Candida infection	30	10	10	20	20		
Candida sepsis	1	1	1				
Cardiac infection	7	7	7				
Cardiac valve vegetation	1	1	1				
Cat scratch disease	2	2	2				
Cavernous sinus thrombosis	1	1	1				
Cellulitis	308	295	296	12	12	1	1
Cellulitis gangrenous	1	1	1				
Cellulitis staphylococcal	1	1	1				
Central nervous system infection	2	2	2				
Cholecystitis infective	4	4	4				
Chorioretinitis	2	2	2				
Chronic sinusitis	4			4	4		
Citrobacter infection	2	2	2				
Clostridial infection	1	1	1				
Clostridium difficile colitis	6	6	6				
Clostridium difficile infection	7	7	7				
Coccidioidomycosis	3	3	3				
Colon gangrene	1	1	1				
Complicated appendicitis	5	5	5				
Conjunctivitis	275	51	51	224	224		
Conjunctivitis bacterial	7	6	6	1	1		
Conjunctivitis viral	6	1	1	5	5		
Corneal infection	2	2	2				

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System Organ Class

Infections and infestations

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Coronavirus infection	33	19	20	13	13		
COVID-19	8101	6171	6172	1927	1929	40	40
COVID-19 pneumonia	316	315	315	1	1	5	5
Creutzfeldt-Jakob disease	6	6	6				
Croup infectious	2	2	2				
Cystitis	165	59	59	106	106		
Cystitis bacterial	3	2	2	1	1		
Cystitis escherichia	1	1	1				
Cystitis klebsiella	1	1	1				
Cytomegalovirus infection	3	3	3				
Cytomegalovirus infection reactivation	4	4	4				
Cytomegalovirus syndrome	1	1	1				
Dacryocystitis	2	2	2				
Dermatitis infected	4	2	2	2	2		
Dermatophytosis of nail	1			1	1		
Dermo-hypodermitis	7	7	7				
Device related infection	5	5	5				
Diabetic foot infection	1			1	1		
Diarrhoea infectious	3	3	3				
Disseminated Bacillus Calmette-Guerin infection	13	13	13				
Disseminated varicella zoster vaccine virus infection	1	1	1				
Disseminated varicella zoster virus infection	15	15	15				
Diverticulitis	65	64	64	1	1		
Diverticulitis intestinal haemorrhagic	2	2	2				
Dysentery	220	217	217	3	3	9	9
Ear infection	150	50	50	100	100		
Ear infection bacterial	2	2	2				

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System Organ Class

Infections and infestations

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Ear infection viral	1			1	1		
Ebola disease	1	1	1				
Eczema herpeticum	6	6	6				
Eczema infected	1	1	1				
Encephalitis	70	70	70				
Encephalitis brain stem	1	1	1				
Encephalitis enteroviral	1	1	1				
Encephalitis viral	7	7	7				
Endocarditis	10	10	10				
Endocarditis bacterial	1	1	1				
Endometritis	1	1	1				
Endophthalmitis	1	1	1				
Enteritis infectious	2	2	2				
Enterobacter bacteraemia	1	1	1				
Enterococcal infection	6	6	6				
Epididymitis	5	5	5				
Epiglottitis	4	4	4				
Epstein-Barr viraemia	1			1	1		
Epstein-Barr virus infection	8	5	5	3	3		
Epstein-Barr virus infection reactivation	10	10	10				
Erysipelas	87	84	84	3	3	1	1
Erysipeloid	1	1	1				
Erythema induratum	2	2	2				
Erythema migrans	2			2	2		
Escherichia bacteraemia	6	6	6				
Escherichia infection	11	11	11				
Escherichia pyelonephritis	1	1	1				

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System Organ Class

Infections and infestations

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Escherichia sepsis	6	6	6				
Escherichia urinary tract infection	13	13	13				
External ear cellulitis	2	2	2				
Eye abscess	1	1	1				
Eye infection	40	18	18	22	22		
Eye infection bacterial	2	2	2				
Eye infection staphylococcal						1	1
Eye infection viral	1			1	1		
Eyelid infection	3	1	1	2	2		
Febrile infection	7	6	6	1	1		
Flea infestation	1			1	1		
Focal peritonitis	2	2	2				
Folliculitis	16	6	6	10	10		
Fungal infection	34	6	6	28	28		
Fungal peritonitis	1	1	1				
Fungal skin infection	7	3	3	4	4		
Furuncle	50	16	16	34	34		
Gangrene	5	5	5				
Gas gangrene	1	1	1				
Gastric infection	3	3	3				
Gastritis bacterial	1	1	1				
Gastritis herpes	1	1	1				
Gastroenteritis	105	38	38	67	67		
Gastroenteritis bacterial	2	2	2				
Gastroenteritis norovirus	1	1	1				
Gastroenteritis rotavirus	1	1	1				
Gastroenteritis viral	45	12	12	33	33		

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System Organ Class

Infections and infestations

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Gastrointestinal bacterial infection	1	1	1				
Gastrointestinal infection	3	2	2	1	1		
Gastrointestinal viral infection	2	1	1	1	1		
Genital abscess	1	1	1				
Genital herpes	69	25	25	44	44		
Genital herpes simplex	7	3	3	4	4		
Genital herpes zoster	7	5	5	2	2		
Genital infection viral	1			1	1		
Gianotti-Crosti syndrome	1			1	1		
Gingival abscess	4	1	1	3	3		
Gingivitis	46	7	7	39	39		
Gonorrhoea	2	2	2				
Groin abscess	1	1	1				
Haematoma infection	3	3	3				
Haemorrhagic fever with renal syndrome	1	1	1				
Haemorrhagic pneumonia	1	1	1				
Haemorrhagic varicella syndrome	1	1	1				
Haemorrhoid infection	1	1	1				
Hand-foot-and-mouth disease	1			1	1		
Helicobacter infection	2	2	2				
Helminthic infection	1	1	1				
Hepatic cyst infection	1	1	1				
Hepatitis A	1	1	1				
Hepatitis B	2	2	2				
Hepatitis C	3	3	3				
Hepatitis D	1	1	1				
Hepatitis E	3	3	3				

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System Organ Class

Infections and infestations

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Hepatitis infectious mononucleosis	1	1	1				
Hepatitis viral	4	4	4				
Herpangina	1			1	1		
Herpes dermatitis	9	3	3	6	6		
Herpes ophthalmic	43	43	43				
Herpes pharyngitis	1	1	1				
Herpes simplex	123	32	32	91	91		
Herpes simplex encephalitis	7	7	7				
Herpes simplex gastritis	1	1	1				
Herpes simplex meningoencephalitis	1	1	1				
Herpes simplex otitis externa	1			1	1		
Herpes simplex reactivation	26	3	3	23	23		
Herpes virus infection	105	31	31	73	74		
Herpes zoster	3208	1244	1244	1964	1964	2	2
Herpes zoster cutaneous disseminated	14	13	13	1	1		
Herpes zoster infection neurological	7	7	7				
Herpes zoster meningitis	4	4	4				
Herpes zoster meningoencephalitis	4	4	4				
Herpes zoster meningoradiculitis	2	2	2				
Herpes zoster oticus	40	40	40			1	1
Herpes zoster pharyngitis	1	1	1				
Herpes zoster reactivation	46	17	17	29	29		
HIV infection	2	2	2				
Hordeolum	45	14	14	31	31		
Human herpesvirus 6 infection	1	1	1				
Iatrogenic infection	1			1	1		
Impetigo	12	6	6	6	6		

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System Organ Class

Infections and Infestations

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Indeterminate leprosy	1	1	1				
Infected bite	1	1	1				
Infected cyst	2	2	2				
Infected dermal cyst	1	1	1				
Infected seroma	1	1	1				
Infected skin ulcer	2	2	2				
Infection	334	183	183	151	151	1	1
Infection in an immunocompromised host	1	1	1				
Infection parasitic	1			1	1		
Infection reactivation	3			3	3		
Infection susceptibility increased	2	2	2				
Infectious mononucleosis	35	16	16	19	19		
Infectious pleural effusion	2	2	2				
Infectious thyroiditis	1			1	1		
Infective exacerbation of bronchiectasis	1	1	1				
Infective exacerbation of chronic obstructive airways disease	6	6	6				
Infective myositis	1	1	1				
Infective pericardial effusion	1	1	1				
Infective tenosynovitis	2	2	2				
Influenza	1779	667	667	1109	1112	8	8
Infusion site infection	1	1	1				
Injection site abscess	5			5	5		
Injection site cellulitis	4	1	1	3	3		
Injection site infection	46			46	46		
Injection site pustule	1	1	1				
Intervertebral discitis	2	2	2				
Intestinal gangrene	1	1	1				

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System Organ Class

Infections and infestations

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Joint abscess	1	1	1				
Kidney infection	46	43	43	3	3		
Klebsiella infection	7	7	7				
Labyrinthitis	93	67	67	26	26		
Lactobacillus infection	1	1	1				
Large intestine infection	4	4	4				
Laryngitis	47	14	14	33	33		
Laryngitis bacterial	1	1	1				
Lip infection	1			1	1		
Listeriosis	2	2	2				
Liver abscess	2	2	2				
Localised infection	55	23	23	32	32		
Lower respiratory tract infection	184	181	181	3	3		
Lower respiratory tract infection bacterial	1	1	1				
Lower respiratory tract infection viral	1	1	1				
Lung abscess	4	4	4				
Lyme disease	19	18	18	1	1		
Lymphadenitis bacterial	2	2	2				
Lymphadenitis viral	1	1	1				
Lymphangitis	42	41	41	1	1		
Lymph gland infection	15	6	6	9	9		
Lymph node abscess	18	18	18				
Lymph node tuberculosis	1	1	1				
Mastitis	67	65	65	2	2		
Mastoiditis	1	1	1				
Measles	11	10	10	1	1		
Mediastinitis	1	1	1				

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System Organ Class

Infections and infestations

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Meningitis	35	35	35				
Meningitis aseptic	23	23	23				
Meningitis bacterial	4	3	3	1	1		
Meningitis herpes	3	3	3				
Meningitis pneumococcal	2	2	2				
Meningitis viral	19	19	19				
Meningoencephalitis herpetic	6	6	6				
Meningomyelitis herpes	1	1	1				
Mononucleosis syndrome	2	1	1	1	1		
Moraxella infection	1	1	1				
Morganella infection	1	1	1				
Mucosal infection	1			1	1		
Mumps	10	5	5	5	5		
Muscle abscess	1	1	1				
Mycoplasma infection	1			1	1		
Myelitis	37	37	37				
Myocarditis infectious	1	1	1				
Myocarditis septic	1	1	1				
Myringitis	1	1	1				
Nail infection	2			2	2		
Nasal abscess	1	1	1				
Nasal herpes	32	5	5	27	27		
Nasal vestibulitis	1	1	1				
Nasopharyngitis	2083	421	421	1662	1662	4	4
Necrotising fasciitis	6	6	6				
Neuroborreliosis	1	1	1				
Neurological infection	1	1	1				

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System Organ Class

Infections and infestations

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Neutropenic sepsis	2	2	2				
Nipple infection	1			1	1		
Norovirus infection	3			3	3		
Omphalitis	1	1	1				
Oophoritis	1	1	1				
Ophthalmic herpes simplex	8	8	8				
Ophthalmic herpes zoster	130	130	130				
Opportunistic infection	1	1	1				
Oral bacterial infection	1	1	1				
Oral candidiasis	54	22	22	32	32		
Oral fungal infection	8	1	1	7	7		
Oral herpes	776	133	133	642	643	1	1
Oral infection	7	1	1	6	6		
Oral pustule	2			2	2		
Oral viral infection	4	1	1	3	3		
Orchitis	13	8	8	5	5		
Oropharyngeal candidiasis	2	1	1	1	1		
Osteomyelitis	7	7	7				
Otitis externa	11	3	3	8	8		
Otitis media	18	5	5	13	13		
Otitis media acute	3			3	3		
Parainfluenzae viral laryngotracheobronchitis	1	1	1				
Parainfluenzae virus infection	1	1	1				
Parapharyngeal space infection	1	1	1				
Paronychia	3			3	3		
Parotitis	36	14	14	22	22		
Parvovirus infection	1			1	1		

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System Organ Class

Infections and infestations

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Pathogen resistance	1	1	1				
Pelvic inflammatory disease	4	4	4				
Perichondritis	3			3	3		
Periodontitis	3	1	1	2	2		
Periorbital abscess	1	1	1				
Periorbital cellulitis	3	3	3				
Periorbital infection	1	1	1				
Peritonitis	12	12	12				
Peritonsillar abscess	4	4	4				
Persistent generalised lymphadenopathy	1	1	1				
Pertussis	5	5	5				
Pharyngeal abscess	4	4	4				
Pharyngeal pustule	1			1	1		
Pharyngitis	118	27	27	91	91	1	1
Pharyngitis bacterial	5	5	5				
Pharyngitis streptococcal	27	8	8	19	19		
Pharyngotonsillitis	5	5	5				
Pilonidal cyst	1			1	1		
Pneumococcal sepsis	1	1	1				
Pneumocystis jirovecii pneumonia	3	3	3				
Pneumonia	822	809	810	12	12	3	3
Pneumonia bacterial	30	30	30				
Pneumonia cytomegaloviral	1	1	1				
Pneumonia fungal	2	2	2				
Pneumonia klebsiella	1	1	1				
Pneumonia legionella	1	1	1				
Pneumonia moraxella	1	1	1				

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System Organ Class

Infections and infestations

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Pneumonia mycoplasmal	2	2	2				
Pneumonia pneumococcal	3	3	3				
Pneumonia pseudomonal	1	1	1				
Pneumonia respiratory syncytial viral	1	1	1				
Pneumonia staphylococcal	4	4	4				
Pneumonia streptococcal	3	3	3				
Pneumonia viral	10	10	10				
Poliomyelitis	1	1	1				
Post-acute COVID-19 syndrome	6	3	3	3	3		
Postoperative wound infection	2	2	2				
Post procedural infection	2	1	1	1	1		
Post viral fatigue syndrome	60	53	53	7	7	1	1
Prion disease	1	1	1				
Progressive multifocal leukoencephalopathy	2	2	2				
Prostate infection	3	3	3				
Prostatic abscess	1	1	1				
Pseudomembranous colitis	1	1	1				
Pseudomonal bacteraemia	2	2	2				
Pseudomonal sepsis	2	2	2				
Pseudomonas infection	3	3	3				
Pulmonary sepsis	10	10	10				
Pulmonary tuberculosis	1	1	1				
Pulpitis dental	13	4	4	9	9		
Purulence	1	1	1				
Purulent discharge	4	1	1	3	3		
Pustule	59	16	16	43	43	1	1
Pyelitis	2	2	2				

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System Organ Class

Infections and infestations

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Pyelonephritis	38	38	38				
Pyelonephritis acute	3	3	3				
Pyuria	1			1	1		
Q fever	19	19	19				
Rash pustular	38	16	16	22	22		
Rectal abscess	1	1	1				
Relapsing fever	2	2	2				
Respiratory tract infection	66	65	65	1	1		
Respiratory tract infection bacterial	3	3	3				
Respiratory tract infection viral	3	1	1	2	2		
Retinitis	1	1	1				
Rhinitis	328	61	61	267	267	1	1
Rhinolaryngitis	1			1	1		
Rhinovirus infection	4	1	1	3	3		
Root canal infection	3			3	3		
Roseola	1			1	1		
Rotavirus infection	2	1	1	1	1		
Rubella	1			1	1		
Salmonellosis	1	1	1				
SARS-CoV-2 sepsis	1	1	1				
Scarlet fever	3	2	2	1	1	1	1
Scrotal infection	1	1	1				
Sebaceous gland infection	1			1	1		
Secondary syphilis	1	1	1				
Secondary transmission	1	1	1				
Sepsis	169	167	167	2	2		
Sepsis syndrome	3	3	3				

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System Organ Class

Infections and infestations

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Septic arthritis staphylococcal	2	2	2				
Septic embolus	1	1	1				
Septic pulmonary embolism	1	1	1				
Septic rash	1	1	1				
Septic shock	56	56	56				
Serratia infection	2	2	2				
Severe acute respiratory syndrome	6	6	6				
Severe invasive streptococcal infection	1	1	1				
Sialoadenitis	20	20	20				
Sinusitis	326	85	85	240	241		
Sinusitis bacterial	3	3	3				
Skin bacterial infection	4	1	1	3	3		
Skin infection	34	11	11	23	23		
Soft tissue infection	5	5	5				
Splenic infection	1	1	1				
Sputum purulent	7	7	7				
Staphylococcal abscess	1			1	1		
Staphylococcal bacteraemia	5	5	5				
Staphylococcal infection	20	19	19	1	1		
Staphylococcal sepsis	6	6	6				
Staphylococcal skin infection	1	1	1				
Streptobacillus infection	2	2	2				
Streptococcal abscess	1	1	1				
Streptococcal bacteraemia	1	1	1				
Streptococcal endocarditis	1	1	1				
Streptococcal infection	11	4	4	7	7		
Streptococcal sepsis	4	4	4				

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System Organ Class

Infections and infestations

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Streptococcal urinary tract infection	1	1	1				
Subcutaneous abscess	18	9	9	9	9		
Superinfection	6	4	4	2	2		
Superinfection bacterial	9	9	9				
Suspected COVID-19	909	558	559	350	350	1	1
Sweating fever	66	66	66				
Syphilis	3	3	3				
Systemic candida	1	1	1				
Tetanus	2	1	1	1	1		
Thrombophlebitis septic	1	1	1				
Tinea infection	1			1	1		
Tinea pedis	1			1	1		
Tinea versicolour	2	1	1	1	1		
Tongue fungal infection	2	1	1	1	1		
Tonsillitis	112	45	45	67	67	1	1
Tonsillitis bacterial	12	12	12				
Tonsillitis streptococcal	3	3	3				
Tooth abscess	23	7	7	16	16		
Tooth infection	42	8	8	34	34		
Toxocariasis	2	2	2				
Toxoplasmosis	2			2	2		
Tracheitis	25	6	6	19	19		
Tracheobronchitis bacterial	2	2	2				
Tuberculosis	4	3	3	1	1		
Upper respiratory tract infection	54	16	16	38	38		
Upper respiratory tract infection bacterial	1	1	1				
Urinary tract candidiasis	1	1	1				

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System Organ Class

Infections and infestations

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Urinary tract infection	497	248	248	249	249	1	1
Urinary tract infection bacterial	17	16	16	1	1		
Urinary tract infection enterococcal	1	1	1				
Urinary tract infection pseudomonal	1	1	1				
Urogenital infection bacterial	1	1	1				
Urosepsis	33	33	33				
Uterine abscess	1	1	1				
Vaccination site abscess	31	9	9	22	22		
Vaccination site cellulitis	110	60	60	50	50		
Vaccination site infection	53	20	20	33	33		
Vaccination site pustule	13	1	1	12	12		
Vaccine breakthrough infection	21	21	21				
Vaginal abscess	1	1	1				
Vaginal infection	15	3	3	12	12		
Varicella	32	12	12	20	20		
Varicella zoster virus infection	13	8	8	5	5		
Vascular device infection	2	2	2				
Vestibular neuronitis	78	61	61	17	17		
Vestibulitis	3	2	2	1	1		
Viraemia	1			1	1		
Viral corneal ulcer	1	1	1				
Viral diarrhoea	1	1	1				
Viral infection	98	47	47	51	51		
Viral keratouveitis	1	1	1				
Viral labyrinthitis	7	3	3	4	4		
Viral myelitis	1	1	1				
Viral myocarditis	3	3	3				

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System Organ Class

Infections and infestations

		Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
Preferred Term	*Total # of Spontaneous AE*	I	C	I	C	I	C
Viral pericarditis	5	5	5				
Viral pharyngitis	16	10	10	6	6		
Viral rash	41	17	17	24	24		
Viral sepsis	3	3	3				
Viral sinusitis	1	1	1				
Viral skin infection	1			1	1		
Viral tonsillitis	1	1	1				
Viral upper respiratory tract infection	4	2	2	2	2		
Virologic failure	2	1	1	1	1		
Vulval abscess	3	3	3				
Vulvitis	3	1	1	2	2		
Vulvovaginal candidiasis	23	11	11	12	12		
Vulvovaginal mycotic infection	10	2	2	8	8		
Wound infection	6	6	6				
Wound infection staphylococcal	1	1	1				
Yellow fever	1	1	1				
Yersinia bacteraemia	1	1	1				
Yersinia infection	1	1	1				
Total:	26600	15624	15630	10961	10970	92	92

System Organ Class

Injury, poisoning and procedural complications

		Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
Preferred Term	*Total # of Spontaneous AE*	I	C	I	C	I	C
Accident	20	10	10	10	10		
Accidental exposure to product	90	2	2	88	88		
Accidental overdose	138	10	11	116	127		

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System Organ Class

Injury, poisoning and procedural complications

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Accidental underdose	14			14	14		
Accident at home	1			1	1		
Adverse event following immunisation	19	13	13	6	6		
Airway burns	3	3	3				
Alcohol poisoning	2	2	2				
Anaesthetic complication	1	1	1				
Anastomotic ulcer	1	1	1				
Animal attack	1			1	1		
Animal bite	8	1	1	7	7		
Ankle fracture	7	6	6	1	1		
Arteriovenous fistula thrombosis	4	4	4				
Arteriovenous graft thrombosis	1	1	1				
Arthropod bite	25	4	4	21	21		
Arthropod sting	16			16	16		
Atypical femur fracture	1	1	1				
Autonomic dysreflexia	3	3	3				
Axillary web syndrome	1			1	1		
Back injury	20	6	6	14	14		
Barotitis media	1			1	1		
Barotrauma	2			2	2		
Bite	10	3	3	7	7		
Bone contusion	3	1	1	2	2		
Bone fragmentation	1	1	1				
Booster dose missed	3			3	3		
Brachial plexus injury	4	4	4				
Brain contusion	5	5	5				
Brain herniation	6	6	6				

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System Organ Class

Injury, poisoning and procedural complications

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Burn oesophageal	5	2	2	3	3		
Burn of internal organs	3	1	1	2	2		
Burn oral cavity	8	8	8				
Burns first degree	1			1	1		
Burns second degree	9	5	5	4	4		
Burns third degree	2	2	2				
Carbon monoxide poisoning	1	1	1				
Cardiac procedure complication	1	1	1				
Cartilage injury	4	3	3	1	1		
Central cord syndrome	1	1	1				
Cerebral hyperperfusion syndrome	1	1	1				
Cerebral ventricle collapse	2	2	2				
Cervical vertebral fracture	1	1	1				
Chemical burn	1			1	1		
Chemical burn of skin	1			1	1		
Chemical cystitis	1			1	1		
Chest crushing	7	7	7				
Chest injury	18	18	18			1	1
Chillblains	98	24	24	74	74		
Circumstance or information capable of leading to device use	21			21	21		
Circumstance or information capable of leading to medicatio	2773	1	1	2771	2772		
Clavicle fracture	7	3	3	4	4		
Cold burn	3	1	1	2	2		
Complications of transplanted kidney	1	1	1				
Compression fracture	3	3	3				
Concussion	39	24	24	15	15		
Conjunctival laceration	1			1	1		

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System Organ Class

Injury, poisoning and procedural complications

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Contraindicated product administered	18	4	4	14	14		
Contraindicated product prescribed	3	1	1	2	2		
Contusion	1246	410	410	836	836	2	2
Corneal abrasion	2	1	1	1	1		
Counterfeit product administered	6			6	6		
Cranial nerve injury	1	1	1				
Craniocerebral injury	19	18	18	1	1		
Craniofacial fracture	1	1	1				
Craniofacial injury	1	1	1				
Decreased embryo viability	1	1	1				
Delayed recovery from anaesthesia	3	2	2	1	1		
Dental restoration failure	3			3	3		
Device use issue	3			3	3		
Dialysis related complication	1	1	1				
Discontinued product administered	2			2	2		
Dose calculation error	2			2	2		
Drug administered in wrong device	1			1	1		
Drug exposure before pregnancy	4	1	1	3	3		
Drug monitoring procedure incorrectly performed	1			1	1		
Ear injury	6	2	2	4	4		
Electric shock	13	3	3	10	10		
Epicondylitis	26	9	9	17	17		
Epidural haemorrhage	1	1	1				
Eschar	4	1	1	3	3		
Expired product administered	214	6	6	208	208		
Exposure during pregnancy	408	49	49	359	359	1	1
Exposure to communicable disease	2			2	2		

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System Organ Class

Injury, poisoning and procedural complications

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Exposure to contaminated water	1			1	1		
Exposure to extreme temperature	2	1	1	1	1		
Exposure to SARS-CoV-2	132	18	18	114	114	1	1
Exposure to toxic agent	1			1	1		
Exposure via body fluid	1			1	1		
Exposure via breast milk	788	112	112	673	676	3	3
Exposure via eye contact	4			4	4		
Exposure via partner	1			1	1		
Exposure via skin contact	53			53	53		
Exposure via unknown route	1			1	1		
Extra dose administered	30	1	1	29	29		
Extradural haematoma	1	1	1				
Eye contusion	43	9	9	34	34	1	1
Eye injury	110	21	21	89	89		
Eyelid contusion	2	1	1	1	1		
Eyelid injury	1	1	1				
Face crushing	2	1	1	1	1		
Face injury	38	24	24	14	14		
Facial bones fracture	20	20	20				
Failed in vitro fertilisation	1	1	1				
Fall	1362	792	792	570	570	3	3
Femoral neck fracture	11	11	11				
Femur fracture	19	19	19				
Foetal exposure during pregnancy	10	3	3	7	7		
Foot fracture	9	8	8	1	1		
Foreign body	1			1	1		
Foreign body aspiration	3	3	3				

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System Organ Class

Injury, poisoning and procedural complications

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Foreign body in eye	1			1	1		
Foreign body in gastrointestinal tract	1	1	1				
Foreign body in mouth	1	1	1				
Foreign body in respiratory tract	1	1	1				
Foreign body in throat	13	13	13				
Foreign body in urogenital tract	1	1	1				
Fracture	21	20	20	1	1		
Fractured skull depressed	1	1	1				
Frostbite	7	2	2	5	5		
Gallbladder injury	1			1	1		
Gastrointestinal injury	1			1	1		
Gastrointestinal stoma complication	2	1	1	1	1		
Gun shot wound	1	1	1				
Hair injury	2			2	2		
Hand fracture	9	9	9				
Head injury	223	144	144	79	79	1	1
Heart injury	22	21	21	1	1		
Heat cramps	4	1	1	3	3		
Heat exhaustion	3			3	3		
Heat illness	8	5	5	3	3		
Heat oedema	8	4	4	4	4		
Heat stroke	12	3	3	9	9		
Hip fracture	22	22	22				
Humerus fracture	5	5	5				
Hyphaema	1	1	1				
Hypobarism	2	1	1	1	1		
Iliotibial band syndrome	1			1	1		

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System Organ Class

Injury, poisoning and procedural complications

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Inadequate aseptic technique in use of product	3			3	3		
Inappropriate schedule of product administration	4548	133	133	4415	4415	1	1
Incision site haemorrhage	1	1	1				
Incision site pain	7	3	3	4	4		
Incision site rash	1			1	1		
Incision site swelling	2			2	2		
Incomplete course of vaccination	64	3	3	61	61		
Incorrect dosage administered	9			9	9		
Incorrect dose administered	322	8	8	312	314		
Incorrect dose administered by device	1			1	1		
Incorrect dose administered by product	1			1	1		
Incorrect product administration duration	5			5	5		
Incorrect product dosage form administered	2			2	2		
Incorrect product formulation administered	3			3	3		
Incorrect route of product administration	858	33	33	816	825		
Inflammation of wound	1			1	1		
Infusion related reaction	4	4	4				
Injection related reaction	38	20	20	18	18		
Injury	68	30	30	38	38		
Injury corneal	2	1	1	1	1		
Intentional device use issue	1			1	1		
Intentional dose omission	21			21	21		
Intentional overdose	6	1	1	5	5		
Intentional product misuse	21			21	21		
Intentional product use issue	8			8	8		
Intentional underdose	1			1	1		
Intercepted medication error	3			3	3		

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System Organ Class

Injury, poisoning and procedural complications

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Intercepted product administration error	2			2	2		
Intercepted product preparation error	2			2	2		
Intoxication by breast feeding	2	2	2				
Jaw fracture	3	3	3				
Joint dislocation	25	16	16	9	9		
Joint injury	87	20	20	67	67		
Lack of vaccination site rotation	2			2	2		
Ligament injury	4			4	4		
Ligament rupture	5	3	3	2	2		
Ligament sprain	46	18	18	28	28		
Limb crushing injury	3	2	2	1	1		
Limb injury	160	50	50	110	110		
Lip injury	18	7	7	11	11		
Liver contusion	1	1	1				
Lower limb fracture	11	10	10	1	1		
Lumbar vertebral fracture	1	1	1				
Mallet finger	1			1	1		
Maternal exposure before pregnancy	27	5	5	22	22		
Maternal exposure during breast feeding	159	68	68	91	91	2	2
Maternal exposure during pregnancy	821	145	145	671	676	26	26
Maternal exposure timing unspecified	74	8	8	66	66		
Medication error	88	9	9	79	79		
Meniscus injury	3	1	1	2	2		
Mouth injury	15	4	4	11	11		
Mucosal excoriation	1			1	1		
Multiple fractures	4	4	4				
Multiple injuries	2	2	2				

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System Organ Class

Injury, poisoning and procedural complications

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Muscle contusion	1			1	1		
Muscle injury	31	14	14	17	17		
Muscle rupture	8	8	8				
Muscle strain	124	48	48	76	76	1	1
Nail avulsion	1			1	1		
Nasal injury	10	4	4	6	6		
Near drowning	2	2	2				
Neck injury	14	4	4	10	10		
Needle fatigue	1			1	1		
Nerve injury	95	51	51	44	44		
Nerve root injury thoracic	1	1	1				
Neurological procedural complication	1			1	1		
Occupational exposure to product	32			32	32		
Occupational exposure to SARS-CoV-2	11	3	3	8	8		
Off label use	4301	138	138	4156	4163	3	3
Optic nerve injury	2	2	2				
Oral contusion	4			4	4		
Oral mucosal scar	1			1	1		
Overdose	1391	34	34	1354	1357		
Palate injury	5	1	1	4	4		
Parasympathetic nerve injury	1	1	1				
Patella fracture	2	2	2				
Paternal exposure before pregnancy	1	1	1				
Paternal exposure during pregnancy	4			4	4		
Paternal exposure timing unspecified	1			1	1		
Pelvic fracture	11	10	10	1	1		
Penis injury	1			1	1		

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System Organ Class

Injury, poisoning and procedural complications

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Periorbital haematoma	9	4	4	5	5		
Periorbital haemorrhage	1			1	1		
Peripheral nerve injury	2	2	2				
Peroneal nerve injury	2	2	2				
Persistent corneal epithelial defect	1			1	1		
Petroleum distillate poisoning	1			1	1		
Phrenic nerve injury	1	1	1				
Pneumocephalus	1	1	1				
Pneumoconiosis	2	2	2				
Poisoning	11	11	11				
Poor quality product administered	5407	9	9	5308	5398		
Post concussion syndrome	2			2	2		
Post laminectomy syndrome	1	1	1				
Post lumbar puncture syndrome	4	1	1	3	3		
Postoperative ileus	1	1	1				
Postoperative wound complication	1	1	1				
Post procedural complication	5	5	5			1	1
Post procedural constipation	1			1	1		
Post procedural haemorrhage	3	3	3			1	1
Post procedural oedema	1			1	1		
Post procedural stroke	1	1	1				
Post-traumatic neck syndrome	5	3	3	2	2		
Post-traumatic pain	1			1	1		
Post vaccination syndrome	3	2	2	1	1		
Prescribed overdose	1			1	1		
Prescribed underdose	1			1	1		
Procedural dizziness	10	5	5	5	5		

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System Organ Class

Injury, poisoning and procedural complications

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Procedural haemorrhage	2	2	2				
Procedural headache	1			1	1		
Procedural nausea	7	5	5	2	2		
Procedural pain	6	3	3	3	3		
Procedural site reaction	1	1	1				
Product administered at inappropriate site	293	13	13	278	280		
Product administered by wrong person	1			1	1		
Product administered to patient of inappropriate age	98	2	2	96	96		
Product administration error	144	6	6	138	138		
Product communication issue	1			1	1		
Product confusion	4			4	4		
Product dispensing error	4			4	4		
Product dispensing issue	4			4	4		
Product dose omission in error	7			7	7		
Product dose omission issue	622	3	3	619	619		
Product label confusion	1725			1724	1725		
Product monitoring error	2			2	2		
Product package associated injury	1			1	1		
Product preparation error	724	8	9	703	715		
Product preparation issue	859	4	5	848	854		
Product prescribing error	20			20	20		
Product prescribing issue	1			1	1		
Product selection error	1			1	1		
Product storage error	576	5	5	571	571		
Product substitution error	1			1	1		
Product use complaint	2			2	2		
Product use in unapproved indication	9	1	1	8	8		

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System Organ Class

Injury, poisoning and procedural complications

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Product use issue	2032	93	93	1931	1939	2	2
Pulmonary contusion	1	1	1				
Radial nerve injury	3	2	2	1	1		
Radiation injury	1			1	1		
Radiation pneumonitis	1			1	1		
Radius fracture	1	1	1				
Reaction to previous exposure to any vaccine	1	1	1				
Recalled product administered	1			1	1		
Recall phenomenon	2			2	2		
Rectal injury	1	1	1				
Respiratory fume inhalation disorder	1	1	1				
Retinal injury	3	3	3				
Rib fracture	32	30	30	2	2		
Road traffic accident	47	30	30	17	17		
Scapula fracture	2	2	2				
Scar	39	18	18	21	21		
Sciatic nerve injury	2	1	1	1	1		
Scratch	78	20	20	58	58		
Scrotal injury	1			1	1		
Sedation complication	1	1	1				
Seroma	1			1	1		
Skeletal injury	4	1	1	3	3		
Skin abrasion	34	13	13	21	21		
Skin injury	14	1	1	13	13		
Skin laceration	47	24	24	23	23		
Skin wound	3	1	1	2	2		
Skull fracture	6	6	6				

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System Organ Class

Injury, poisoning and procedural complications

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Skull fractured base	3	3	3				
Soft tissue foreign body	1			1	1		
Soft tissue injury	3	2	2	1	1		
Spinal column injury	2	1	1	1	1		
Spinal compression fracture	6	6	6				
Spinal cord injury	4	4	4				
Spinal cord injury cauda equina	1	1	1				
Spinal cord injury sacral	1			1	1		
Spinal fracture	6	6	6				
Splenic injury	1	1	1				
Splenic rupture	5	5	5				
Splinter	2			2	2		
Sports injury	1			1	1		
Stab wound	1			1	1		
Sternal fracture	1	1	1				
Stoma site discharge	1	1	1				
Stoma site extravasation	1			1	1		
Stoma site haemorrhage	5	5	5				
Stoma site pain	2	1	1	1	1		
Stoma site pruritus	1			1	1		
Stress fracture	1			1	1		
Subcutaneous haematoma	17	8	8	9	9		
Subdural haematoma	36	36	36				
Subdural haemorrhage	9	9	9				
Sunburn	42	7	7	35	35		
Superficial injury of eye	3	1	1	2	2		
Suture related complication	1	1	1				

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System Organ Class

Injury, poisoning and procedural complications

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Synovial rupture	2	1	1	1	1		
Tendon injury	10	8	8	2	2		
Tendon rupture	13	7	7	6	6		
Thermal burn	35	14	14	21	21		
Thermal burns of eye	15	14	14	1	1		
Thoracic vertebral fracture	2	2	2				
Tibia fracture	1	1	1				
Tissue injury	1	1	1				
Tongue injury	8	2	2	6	6		
Tooth avulsion	2	2	2				
Tooth fracture	14	5	5	9	9		
Tooth injury	12	5	5	7	7		
Toxic anterior segment syndrome	1	1	1				
Toxicity to various agents	16	14	14	2	2	1	1
Tracheal deviation	1	1	1				
Tracheal haemorrhage	1	1	1				
Tracheal obstruction	5	5	5				
Transcription medication error	1			1	1		
Transfusion reaction	1			1	1		
Transplant failure	2	2	2				
Traumatic fracture	1	1	1				
Traumatic haematoma	6	5	5	1	1		
Traumatic haemorrhage	3	3	3				
Traumatic intracranial haemorrhage	3	3	3				
Traumatic lung injury	4			4	4		
Trunk injury	1			1	1		
Ulnar nerve injury	6	5	5	1	1		

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System Organ Class

Injury, poisoning and procedural complications

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Underdose	614	5	5	597	609		
Upper limb fracture	20	18	18	2	2		
Vaccination complication	655	72	72	583	583	5	5
Vaccination error	41	3	3	38	38		
Vascular access site swelling	1			1	1		
Vascular graft thrombosis	4	4	4				
Vascular injury	13	7	7	6	6		
Vasoplegia syndrome	4	4	4				
Venous injury	3	3	3				
VIIIth nerve injury	1	1	1				
VIIth nerve injury	1	1	1				
Vth nerve injury	1	1	1				
Vulvovaginal injury	1	1	1				
Wound	62	29	29	33	33	1	1
Wound complication	11	3	3	8	8		
Wound haemorrhage	15	7	7	8	8		
Wound necrosis	2	2	2				
Wound secretion	5	4	4	1	1		
Wrist fracture	9	9	9				
Wrong dose	4			4	4		
Wrong drug	5			5	5		
Wrong patient received product	2			2	2		
Wrong product administered	285	7	7	278	278		
Wrong product stored	5			5	5		
Wrong schedule	16			16	16		
Wrong technique in device usage process	3			3	3		
Wrong technique in product usage process	467	7	7	456	460		

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System Organ Class

Injury, poisoning and procedural complications

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Total:	37590	3705	3708	33706	33882	57	57

System Organ Class

Investigations

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Acoustic stimulation tests	1	1	1				
Activated partial thromboplastin time abnormal	1	1	1				
Activated partial thromboplastin time prolonged	29	20	20	9	9		
Activated partial thromboplastin time ratio decreased	1			1	1		
Activated partial thromboplastin time ratio increased	1			1	1		
Activated partial thromboplastin time shortened	10	6	6	4	4		
Adjusted calcium decreased	1	1	1				
Alanine aminotransferase	1			1	1		
Alanine aminotransferase abnormal	3	1	1	2	2		
Alanine aminotransferase decreased	4	1	1	3	3		
Alanine aminotransferase increased	99	43	43	56	56		
Albumin CSF increased	1	1	1				
Albumin globulin ratio decreased	1			1	1		
Albumin globulin ratio increased	1			1	1		
Alcohol test false positive	1			1	1		
Aldolase increased	1			1	1		
Allergy test positive	1			1	1		
Alpha-1 anti-trypsin increased	1	1	1				
Alpha 1 globulin decreased	1	1	1				
Alpha 2 globulin decreased	1	1	1				
Alpha globulin increased	1			1	1		

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System Organ Class

Investigations

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Alpha tumour necrosis factor increased	1	1	1				
Amino acid level decreased	1			1	1		
Amino acid level increased	1			1	1		
Ammonia abnormal	1			1	1		
Ammonia increased	1	1	1				
Amphetamines positive	1			1	1		
Amylase decreased	1			1	1		
Amylase increased	13	6	6	7	7		
Analgesic drug level	1	1	1				
Analgesic drug level above therapeutic	1	1	1				
Angiotensin converting enzyme increased	1	1	1				
Anion gap abnormal	1			1	1		
Anion gap decreased	1			1	1		
Anion gap increased	2			2	2		
Antibody test	1			1	1		
Antibody test abnormal	34			34	34		
Antibody test negative	17	3	3	14	14		
Antibody test normal	1			1	1		
Antibody test positive	2			2	2		
Anticoagulation drug level above therapeutic	1			1	1		
Anticoagulation drug level below therapeutic	8	2	2	6	6		
Anticoagulation drug level increased	1	1	1				
Anti-cyclic citrullinated peptide antibody positive	1	1	1				
Anti factor VIII antibody positive	2	2	2				
Anti Kell antibody test positive	1			1	1		
Anti-myelin-associated glycoprotein antibodies positive	1	1	1				
Antineutrophil cytoplasmic antibody positive	1			1	1		

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System Organ Class

Investigations

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Antinuclear antibody	1	1	1				
Antinuclear antibody increased	2			2	2		
Antinuclear antibody positive	12	4	4	8	8		
Antiphospholipid antibodies positive	4	4	4				
Anti-platelet antibody	1	1	1				
Antipsychotic drug level below therapeutic	1			1	1		
Antipsychotic drug level increased	1	1	1				
Anti-thyroid antibody	1			1	1		
Anti-thyroid antibody positive	5	2	2	3	3		
Aortic bruit	1			1	1		
Arteriogram abnormal	1	1	1				
Arteriogram coronary normal	1	1	1				
Aspartate aminotransferase	1			1	1		
Aspartate aminotransferase abnormal	2	1	1	1	1		
Aspartate aminotransferase decreased	1			1	1		
Aspartate aminotransferase increased	62	24	24	38	38		
Aspiration joint	1			1	1		
AST/ALT ratio abnormal	2			2	2		
Atrial pressure increased	1			1	1		
Audiogram abnormal	3	1	1	2	2		
Auscultation	1			1	1		
Autoantibody negative	1	1	1				
Bacterial test	1	1	1				
Bacterial test positive	14	7	7	7	7		
Band neutrophil count increased	1	1	1				
Base excess decreased	1			1	1		
Basophil count abnormal	1			1	1		

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System Organ Class

Investigations

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Basophil count decreased	2			2	2		
Basophil count increased	3			3	3		
Basophil percentage increased	1			1	1		
Beta 2 microglobulin increased	1			1	1		
Beta globulin increased	1			1	1		
Bile output increased	1	1	1				
Bilirubin conjugated increased	3	1	1	2	2		
Bilirubin urine present	1			1	1		
Biopsy	1			1	1		
Biopsy bone marrow abnormal	1	1	1				
Biopsy lymph gland	1			1	1		
Biopsy muscle abnormal	1	1	1				
Blast cell count increased	1	1	1				
Bleeding time abnormal	2	1	1	1	1		
Bleeding time prolonged	3	3	3				
Bleeding time shortened	1			1	1		
Blood 25-hydroxycholecalciferol decreased	1			1	1		
Blood albumin decreased	10	1	1	9	9		
Blood albumin increased	2	1	1	1	1		
Blood alcohol decreased	2	1	1	1	1		
Blood alcohol increased	3	2	2	1	1		
Blood alkaline phosphatase	1			1	1		
Blood alkaline phosphatase decreased	2			2	2		
Blood alkaline phosphatase increased	29	11	11	18	18		
Blood antidiuretic hormone increased	1	1	1				
Blood bactericidal activity	1			1	1		
Blood bicarbonate decreased	5	2	2	3	3		

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System Organ Class

Investigations

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Blood bicarbonate increased	1			1	1		
Blood bilirubin abnormal	2	1	1	1	1		
Blood bilirubin decreased	3			3	3		
Blood bilirubin increased	37	12	12	25	25		
Blood bilirubin unconjugated increased	1			1	1		
Blood calcium abnormal	3	2	2	1	1		
Blood calcium decreased	19	2	2	17	17		
Blood calcium increased	5	1	1	4	4		
Blood chloride decreased	5	1	1	4	4		
Blood chloride increased	11	2	2	9	9		
Blood cholesterol	2			2	2		
Blood cholesterol abnormal	5			5	5		
Blood cholesterol decreased	4			4	4		
Blood cholesterol increased	48	12	12	36	36		
Blood cholinesterase decreased	1			1	1		
Blood chromium increased	1	1	1				
Blood copper increased	2			2	2		
Blood count	1			1	1		
Blood count abnormal	19	5	5	14	14		
Blood creatine increased	5	2	2	3	3		
Blood creatine phosphokinase abnormal	2	1	1	1	1		
Blood creatine phosphokinase increased	75	45	45	30	30		
Blood creatine phosphokinase MB increased	5	2	2	3	3		
Blood creatinine abnormal	4	2	2	2	2		
Blood creatinine decreased	11	1	1	10	10		
Blood creatinine increased	63	20	20	43	43		
Blood culture positive	1	1	1				

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System Organ Class

Investigations

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Blood electrolytes decreased	3	3	3				
Blood electrolytes increased	1			1	1		
Blood fibrinogen abnormal	1	1	1				
Blood fibrinogen decreased	5	3	3	2	2		
Blood fibrinogen increased	23	4	4	19	19		
Blood folate decreased	7	3	3	4	4		
Blood folate increased	1			1	1		
Blood follicle stimulating hormone increased	2	2	2				
Blood gases abnormal	4	4	4				
Blood glucose	3	2	2	1	1		
Blood glucose abnormal	45	17	17	28	28		
Blood glucose decreased	147	60	60	87	87		
Blood glucose fluctuation	58	20	20	38	38		
Blood glucose increased	423	153	153	270	270		
Blood growth hormone abnormal	2			2	2		
Blood heavy metal increased	1			1	1		
Blood immunoglobulin A increased	2	1	1	1	1		
Blood immunoglobulin E increased	6	3	3	3	3		
Blood immunoglobulin G	2			2	2		
Blood immunoglobulin G abnormal	2			2	2		
Blood immunoglobulin G decreased	8			8	8		
Blood immunoglobulin G increased	8	2	2	6	6		
Blood immunoglobulin M abnormal	2	1	1	1	1		
Blood immunoglobulin M decreased	3	1	1	2	2		
Blood immunoglobulin M increased	6			6	6		
Blood insulin increased	1			1	1		
Blood iron	1			1	1		

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System Organ Class

Investigations

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Blood iron decreased	25	13	13	12	12		
Blood iron increased	4	1	1	3	3		
Blood ketone body	2	1	1	1	1		
Blood ketone body increased	3	2	2	1	1		
Blood ketone body present	1	1	1				
Blood lactate dehydrogenase abnormal	1			1	1		
Blood lactate dehydrogenase increased	33	14	14	19	19		
Blood lactic acid	1			1	1		
Blood lactic acid decreased	2			2	2		
Blood lactic acid increased	28	13	13	15	15		
Blood luteinising hormone abnormal	1			1	1		
Blood magnesium decreased	9	4	4	5	5		
Blood magnesium increased	2			2	2		
Blood methaemoglobin present	1			1	1		
Blood oestrogen abnormal	1			1	1		
Blood oestrogen increased	1	1	1				
Blood osmolarity decreased	1			1	1		
Blood osmolarity increased	2			2	2		
Blood parathyroid hormone decreased	1			1	1		
Blood parathyroid hormone increased	3			3	3		
Blood pH	4	3	3	1	1		
Blood pH abnormal	1	1	1				
Blood pH decreased	1	1	1				
Blood pH increased	5	3	3	2	2		
Blood phosphorus decreased	8	4	4	4	4		
Blood phosphorus increased	3	1	1	2	2		
Blood potassium abnormal	2	2	2				

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System Organ Class

Investigations

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Blood potassium decreased	53	24	24	29	29		
Blood potassium increased	18	6	6	12	12		
Blood pressure abnormal	220	68	68	152	152		
Blood pressure ambulatory abnormal	2	2	2				
Blood pressure ambulatory increased	8	1	1	7	7		
Blood pressure decreased	825	443	443	382	382	2	2
Blood pressure diastolic	1			1	1		
Blood pressure diastolic abnormal	1	1	1				
Blood pressure diastolic decreased	32	10	10	22	22		
Blood pressure diastolic increased	44	17	17	27	27		
Blood pressure immeasurable	12	10	10	2	2		
Blood pressure increased	3179	1477	1479	1693	1700	7	7
Blood pressure measurement	11	2	2	9	9		
Blood pressure normal	1	1	1				
Blood pressure orthostatic abnormal	2	2	2				
Blood pressure orthostatic decreased	4	2	2	2	2		
Blood pressure orthostatic increased	1			1	1		
Blood pressure systolic	3	2	2	1	1		
Blood pressure systolic abnormal	2	1	1	1	1		
Blood pressure systolic decreased	25	12	12	13	13		
Blood pressure systolic increased	175	101	101	74	74		
Blood prolactin increased	2			2	2		
Blood smear test abnormal	1			1	1		
Blood sodium decreased	43	17	17	26	26		
Blood sodium increased	8	3	3	5	5		
Blood test	2	1	1	1	1		
Blood test abnormal	43	20	20	23	23	1	1

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System Organ Class

Investigations

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Blood testosterone decreased	1			1	1		
Blood testosterone increased	1			1	1		
Blood thrombin	1	1	1				
Blood thyroid stimulating hormone abnormal	1			1	1		
Blood thyroid stimulating hormone decreased	9	4	4	5	5		
Blood thyroid stimulating hormone increased	30	8	8	22	22		
Blood triglycerides abnormal	1			1	1		
Blood triglycerides decreased	2			2	2		
Blood triglycerides increased	13	4	4	9	9		
Blood urea abnormal	2			2	2		
Blood urea decreased	2	2	2				
Blood urea increased	37	8	8	29	29		
Blood uric acid abnormal	1			1	1		
Blood uric acid increased	12	4	4	8	8		
Blood urine	16	8	8	8	8		
Blood urine present	120	43	43	77	77		
Blood viscosity increased	1			1	1		
Blood zinc decreased	1			1	1		
B-lymphocyte count decreased	1			1	1		
Body height decreased	42	1	1	41	41		
Body mass index increased	2			2	2		
Body temperature	121	20	20	101	101		
Body temperature abnormal	219	70	70	149	149		
Body temperature decreased	219	66	66	153	153		
Body temperature fluctuation	104	36	36	68	68		
Body temperature increased	3921	348	348	3569	3573	6	6
Body temperature normal	3			3	3		

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System Organ Class

Investigations

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Bone density abnormal	1			1	1		
Bone density decreased	1			1	1		
Brain natriuretic peptide increased	16	10	10	6	6		
Brain scan abnormal	2	2	2				
Breath sounds	3	1	1	2	2		
Breath sounds abnormal	46	29	29	17	17		
Calcium ionised decreased	1			1	1		
Calcium ionised increased	1			1	1		
Capillary nail refill test abnormal	4	1	1	3	3		
Carbohydrate antigen 125 increased	2			2	2		
Carbohydrate antigen 19-9 increased	1	1	1				
Carbon dioxide decreased	1	1	1				
Carbon dioxide increased	2	1	1	1	1		
Carcinoembryonic antigen increased	5	5	5				
Cardiac function test abnormal	1			1	1		
Cardiac murmur	19	12	12	7	7		
Cardiac output	1			1	1		
Cardio-ankle vascular index	1			1	1		
Cardiothoracic ratio increased	2	1	1	1	1		
Carotid bruit	3	3	3				
Carotid pulse	1	1	1				
Catheterisation cardiac	1	1	1				
CD4 lymphocytes decreased	3	2	2	1	1		
Cell marker decreased	1	1	1				
Cells in urine	1	1	1				
Central venous pressure abnormal	1			1	1		
Chest expansion decreased	1			1	1		

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System Organ Class

Investigations

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Chest X-ray	2	1	1	1	1		
Chest X-ray abnormal	11	8	8	3	3		
Clostridium test positive	2	2	2				
Clot retraction	1	1	1				
Coagulation factor decreased	1			1	1		
Coagulation factor increased	2	2	2				
Coagulation factor VIII level decreased	2	1	1	1	1		
Coagulation factor VIII level increased	1			1	1		
Coagulation test abnormal	1			1	1		
Coagulation time prolonged	7	4	4	3	3		
Coagulation time shortened	1	1	1				
Coma scale abnormal	16	15	15	1	1		
Complement factor C1 increased	1			1	1		
Complement factor C3 decreased	1			1	1		
Complement factor C3 increased	3	1	1	2	2		
Complement factor decreased	1			1	1		
Complement factor increased	1			1	1		
Computerised tomogram abnormal	1	1	1				
Computerised tomogram normal	1			1	1		
Computerised tomogram thorax abnormal	1			1	1		
Corneal reflex decreased	8	5	5	3	3		
Coronavirus test positive	8	5	5	3	3		
Cortisol decreased	4	3	3	1	1		
Cortisol increased	1	1	1				
C-reactive protein	2	1	1	1	1		
C-reactive protein abnormal	10	6	6	4	4		
C-reactive protein decreased	3	1	1	2	2		

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System Organ Class

Investigations

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
C-reactive protein increased	476	235	235	241	241		
Creatinine renal clearance abnormal	1			1	1		
Creatinine renal clearance decreased	4	3	3	1	1		
Cryoglobulins present	1			1	1		
Crystal urine	1			1	1		
CSF cell count increased	2	2	2				
CSF glucose increased	2	2	2				
CSF immunoglobulin increased	1	1	1				
CSF lymphocyte count increased	1	1	1				
CSF oligoclonal band present	1	1	1				
CSF polymorphonuclear cell count increased	1	1	1				
CSF pressure	1	1	1				
CSF protein increased	9	9	9				
CSF test abnormal	3	3	3				
CSF volume increased	1			1	1		
Culture negative	1	1	1				
Culture urine positive	2			2	2		
Cytogenetic analysis abnormal	1	1	1				
Cytokine abnormal	1			1	1		
Cytomegalovirus test positive	4	1	1	3	3		
Dermatologic examination abnormal	1	1	1				
Differential white blood cell count abnormal	1	1	1				
Digestive enzyme abnormal	2			2	2		
Double stranded DNA antibody positive	1	1	1				
Drug level decreased	2	1	1	1	1		
Drug level fluctuating	1	1	1				
Drug level increased	3	1	1	2	2		

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System Organ Class

Investigations

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Drug screen positive	2	1	1	1	1		
Drug specific antibody	1			1	1		
Ear, nose and throat examination abnormal	1			1	1		
Eastern Cooperative Oncology Group performance status wo	1			1	1		
Echocardiogram	1	1	1				
Echocardiogram abnormal	2	2	2				
Ejection fraction abnormal	8	6	6	2	2		
Ejection fraction decreased	11	10	10	1	1		
Electrocardiogram	1			1	1		
Electrocardiogram abnormal	53	29	29	24	24	1	1
Electrocardiogram change	7	4	4	3	3		
Electrocardiogram PR prolongation	1	1	1				
Electrocardiogram PR shortened	1	1	1				
Electrocardiogram P wave abnormal	1			1	1		
Electrocardiogram QRS complex prolonged	5	5	5				
Electrocardiogram QRS complex shortened	4	4	4				
Electrocardiogram QT interval abnormal	2	2	2				
Electrocardiogram QT prolonged	9	9	9				
Electrocardiogram repolarisation abnormality	7	7	7				
Electrocardiogram ST segment abnormal	4	3	3	1	1		
Electrocardiogram ST segment depression	12	12	12				
Electrocardiogram ST segment elevation	25	25	25				
Electrocardiogram ST-T change	2	2	2				
Electrocardiogram ST-T segment abnormal	1	1	1				
Electrocardiogram ST-T segment depression	1	1	1				
Electrocardiogram T wave abnormal	2			2	2		
Electrocardiogram T wave inversion	13	13	13			1	1

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System Organ Class

Investigations

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Electrocardiogram T wave peaked	2			2	2		
Electroencephalogram abnormal	3	2	2	1	1		
Electromyogram abnormal	1			1	1		
Emergency care examination	1	1	1				
Enzyme level increased	1	1	1				
Eosinophil count abnormal	1			1	1		
Eosinophil count decreased	12	3	3	9	9		
Eosinophil count increased	24	10	10	14	14		
Eosinophil percentage increased	2	1	1	1	1		
Epinephrine abnormal	1			1	1		
Epinephrine increased	7	2	2	5	5		
Epstein-Barr virus antibody	1			1	1		
Epstein-Barr virus antibody positive	4	2	2	2	2		
Epstein-Barr virus antigen positive	1			1	1		
Epstein-Barr virus test positive	3	1	1	2	2		
Escherichia test positive	3	1	1	2	2		
Exercise electrocardiogram abnormal	2	1	1	1	1		
Faecal calprotectin	1	1	1				
Faecal calprotectin decreased	1			1	1		
Faecal calprotectin increased	6	3	3	3	3		
Faecal volume decreased	1			1	1		
Faecal volume increased	1			1	1		
False negative investigation result	1	1	1				
False positive investigation result	3	1	1	2	2		
Fibrin	1			1	1		
Fibrin D dimer increased	227	122	122	105	105	1	1
Fibrin degradation products increased	1	1	1				

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System Organ Class

Investigations

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Fibrinolysis	1	1	1				
Fibrinolysis abnormal	1	1	1				
Fibroblast growth factor 23	1			1	1		
Fibroblast growth factor 23 increased	1			1	1		
Foetal heart rate abnormal	6	5	5	1	1		
Foetal heart rate decreased	1	1	1				
Foetal heart rate increased	1			1	1		
Forced expiratory flow	1	1	1				
Forced expiratory volume increased	2	2	2				
Foveal reflex abnormal	1	1	1				
Full blood count	1			1	1		
Full blood count abnormal	6	3	3	3	3		
Full blood count increased	3	1	1	2	2		
Gamma-glutamyltransferase increased	46	16	16	30	30		
Gastric pH decreased	7	1	1	6	6		
General physical condition	1			1	1		
General physical condition abnormal	20	10	10	10	10		
General physical condition normal	1			1	1		
Glomerular filtration rate abnormal	2	1	1	1	1		
Glomerular filtration rate decreased	44	16	16	28	28		
Glomerular filtration rate increased	1			1	1		
Glucose urine present	3	2	2	1	1		
Glutamate dehydrogenase increased	1			1	1		
Glycosylated haemoglobin abnormal	1			1	1		
Glycosylated haemoglobin decreased	2			2	2		
Glycosylated haemoglobin increased	14	6	6	8	8		
Granulocyte count decreased	2			2	2		

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System Organ Class

Investigations

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Granulocyte count increased	1			1	1		
Granulocytes abnormal	1			1	1		
Grip strength	1	1	1				
Grip strength decreased	93	43	43	50	50		
Gustometry	1			1	1		
Haematocrit decreased	36	3	3	33	33		
Haematocrit increased	11	3	3	8	8		
Haematology test abnormal	4	2	2	2	2		
Haemoglobin	1	1	1				
Haemoglobin abnormal	3	1	1	2	2	1	1
Haemoglobin decreased	133	63	63	70	70		
Haemoglobin increased	10	3	3	7	7		
Haemoglobin urine present	1			1	1		
Haptoglobin decreased	2	2	2				
Haptoglobin increased	2	1	1	1	1		
Head lag	2	2	2				
Heart rate	42	19	19	23	23		
Heart rate abnormal	166	71	71	95	95	1	1
Heart rate decreased	272	146	147	125	125		
Heart rate increased	2952	1062	1065	1880	1887	2	2
Heart rate irregular	287	131	131	156	156	1	1
Heart rate normal	2			2	2		
Heart rate variability increased	1	1	1				
Heart sounds	1	1	1				
Heart sounds abnormal	11	4	4	7	7		
Heparin-induced thrombocytopenia test positive	2	1	1	1	1		
Hepatic enzyme abnormal	16	10	10	6	6		

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System Organ Class

Investigations

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Hepatic enzyme increased	65	32	32	33	33	2	2
Hepatitis A antibody positive	1			1	1		
Hepatitis A virus test positive	1			1	1		
Hepatitis B antibody positive	1			1	1		
Hepatitis B virus test positive	1			1	1		
Herpes simplex test positive	3	1	1	2	2		
Herpes virus test	1			1	1		
High density lipoprotein decreased	3			3	3		
High density lipoprotein increased	3			3	3		
Histamine abnormal	1			1	1		
Histamine level increased	7	1	1	6	6		
HIV antibody positive	2			2	2		
HIV test	1	1	1				
HIV test false positive	4			4	4		
HIV test negative	1	1	1				
HIV test positive	3	1	1	2	2		
HLA-B*27 assay	1			1	1		
Hoover's sign of leg paresis	1	1	1				
Hormone level abnormal	28	12	12	16	16	1	1
Human chorionic gonadotropin increased	1	1	1				
Human epidermal growth factor receptor decreased	1	1	1				
Hysteroscopy	1	1	1				
Iliac bruit	1	1	1				
Imaging procedure abnormal	1	1	1				
Immature granulocyte count increased	2			2	2		
Immunoglobulins abnormal	2			2	2		
Immunoglobulins decreased	2			2	2		

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Investigations

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Immunoglobulins increased	7	1	1	6	6		
Immunology test	3	1	1	2	2		
Immunology test abnormal	2			2	2		
Inflammatory marker decreased	2			2	2		
Inflammatory marker increased	48	27	27	21	21		
Influenza A virus test positive	1			1	1		
Influenza B virus test positive	1			1	1		
Inspiratory capacity abnormal	2			2	2		
Inspiratory capacity decreased	6	3	3	3	3		
Interleukin level increased	3	2	2	1	1		
International normalised ratio abnormal	8	4	4	4	4		
International normalised ratio decreased	42	20	20	22	22		
International normalised ratio fluctuation	5	3	3	2	2		
International normalised ratio increased	123	67	67	56	56		
Intestinal transit time increased	1			1	1		
Intraocular pressure increased	30	11	11	19	19		
Intraocular pressure test abnormal	4			4	4		
Iodine uptake decreased	1			1	1		
Iodine uptake increased	1	1	1				
Iron binding capacity total abnormal	1	1	1				
Laboratory test abnormal	17	7	7	10	10		
Laboratory test interference	1			1	1		
Laboratory test normal	1			1	1		
Left ventricular end-diastolic pressure increased	1	1	1				
Leukocyte alkaline phosphatase increased	1	1	1				
Light chain analysis increased	1			1	1		
Limb girth decreased	1			1	1		

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Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Lipase decreased	2			2	2		
Lipase increased	20	7	7	13	13		
Lipids abnormal	1			1	1		
Lipids increased	6	1	1	5	5		
Listeria test positive	1			1	1		
Liver function test	1			1	1		
Liver function test abnormal	52	36	36	16	16		
Liver function test increased	40	21	21	19	19		
Low density lipoprotein increased	20	5	5	15	15		
Lumbar puncture	1	1	1				
Lumbar puncture abnormal	1	1	1				
Lymph node palpable	64	6	6	58	58		
Lymph nodes scan abnormal	4	2	2	2	2		
Lymphoblast count	1			1	1		
Lymphocyte count	2			2	2		
Lymphocyte count abnormal	3	1	1	2	2		
Lymphocyte count decreased	45	11	11	34	34		
Lymphocyte count increased	24	8	8	16	16		
Lymphocyte morphology abnormal	1			1	1		
Lymphocyte percentage decreased	5			5	5		
Lymphocyte percentage increased	1			1	1		
Magnetic resonance imaging abnormal	3	3	3				
Magnetic resonance imaging head	3			3	3		
Magnetic resonance imaging head abnormal	8	6	6	2	2		
Mammogram abnormal	2			2	2		
Mast cell degranulation present	1			1	1		
Matrix metalloproteinase-3 increased	1			1	1		

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Investigations

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Mean arterial pressure increased	5	1	1	4	4		
Mean cell haemoglobin	2			2	2		
Mean cell haemoglobin concentration decreased	8			8	8		
Mean cell haemoglobin concentration increased	6			6	6		
Mean cell haemoglobin decreased	8	2	2	6	6		
Mean cell haemoglobin increased	6			6	6		
Mean cell volume decreased	8	2	2	6	6		
Mean cell volume increased	9	2	2	7	7		
Mean platelet volume decreased	6	1	1	5	5		
Mean platelet volume increased	3			3	3		
Mediastinoscopy	1	1	1				
Megakaryocytes increased	1	1	1				
Menstruation normal	1			1	1		
Metabolic function test abnormal	3	1	1	2	2		
Metamyelocyte count increased	2	1	1	1	1		
Mini mental status examination abnormal	1	1	1				
Misleading laboratory test result	1			1	1		
Monoclonal immunoglobulin increased	1	1	1				
Monocyte count abnormal	1			1	1		
Monocyte count decreased	7	1	1	6	6		
Monocyte count increased	24	2	2	22	22		
Monocyte percentage increased	2			2	2		
Muscle strength abnormal	18	5	5	13	13		
Mycobacterium tuberculosis complex test positive	1			1	1		
Myelocyte count increased	2	1	1	1	1		
Myocardial necrosis marker increased	20	19	19	1	1		
Myocardial strain	1	1	1				

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System Organ Class

Investigations

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Myoglobin blood increased	2	2	2				
Natural killer T cell count increased	1			1	1		
Nerve conduction studies abnormal	2	1	1	1	1		
Neurological examination abnormal	1	1	1				
Neurological examination normal	1			1	1		
Neutralising antibodies	1			1	1		
Neutralising antibodies negative	1			1	1		
Neutrophil count abnormal	9	4	4	5	5	1	1
Neutrophil count decreased	38	16	16	22	22		
Neutrophil count increased	50	6	6	44	44		
Neutrophil/lymphocyte ratio decreased	1			1	1		
Neutrophil morphology abnormal	1	1	1				
Neutrophil percentage increased	3	1	1	2	2		
NIH stroke scale score decreased	1	1	1				
Nitrite urine present	4			4	4		
Norepinephrine increased	1			1	1		
N-terminal prohormone brain natriuretic peptide increased	16	10	10	6	6		
Occult blood positive	2	1	1	1	1		
Ophthalmological examination abnormal	1			1	1		
Opiates	1			1	1		
Opiates positive	1	1	1				
Orthopaedic examination abnormal	1	1	1				
Orthostatic heart rate response increased	1			1	1		
Oxygen consumption	2			2	2		
Oxygen consumption decreased	8	4	4	4	4		
Oxygen consumption increased	1			1	1		
Oxygen saturation	8	4	4	4	4		

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System Organ Class

Investigations

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Oxygen saturation abnormal	42	16	16	26	26	1	1
Oxygen saturation decreased	1083	797	798	285	285	4	4
Oxygen saturation immeasurable	3	3	3				
Oxygen saturation increased	2	2	2				
Oxygen saturation normal	2	1	1	1	1		
Palpatory finding abnormal	1			1	1		
Pancreatic enzymes decreased	1			1	1		
Pancreatic enzymes increased	1			1	1		
Parvovirus B19 test positive	2	1	1	1	1		
PCO2 abnormal	1	1	1				
PCO2 decreased	3			3	3		
PCO2 increased	4	1	1	3	3		
Peak expiratory flow rate	1	1	1				
Peak expiratory flow rate abnormal	1	1	1				
Peak expiratory flow rate decreased	7	7	7				
Peritoneal effluent leukocyte count increased	1			1	1		
pH urine	2	1	1	1	1		
pH urine abnormal	1	1	1				
pH urine increased	1	1	1				
Physical examination abnormal	2	1	1	1	1		
Plasma cells increased	1			1	1		
Plasma viscosity abnormal	1	1	1				
Platelet aggregation abnormal	1			1	1		
Platelet count abnormal	10	4	4	6	6		
Platelet count decreased	277	154	154	123	123	1	1
Platelet count increased	58	18	18	40	40		
Plateletcrit increased	1			1	1		

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System Organ Class

Investigations

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Platelet function test abnormal	1			1	1		
PO2	2			2	2		
PO2 decreased	16	7	7	9	9		
PO2 increased	1	1	1				
Polymerase chain reaction positive	13	7	7	6	6		
Pregnancy test	1			1	1		
Pregnancy test negative	1			1	1		
Pregnancy test positive	1			1	1		
Procalcitonin decreased	1			1	1		
Procalcitonin increased	11	6	6	5	5		
Product residue present	2	1	1	1	1		
Prohormone brain natriuretic peptide increased	3	2	2	1	1		
Prostatic specific antigen decreased	1			1	1		
Prostatic specific antigen increased	11	4	4	7	7		
Protein C increased	4	3	3	1	1		
Protein total decreased	10			10	10		
Protein total increased	6			6	6		
Protein urine	2	1	1	1	1		
Protein urine present	9	3	3	6	6		
Prothrombin level abnormal	1	1	1				
Prothrombin level decreased	2	1	1	1	1		
Prothrombin level increased	3	2	2	1	1		
Prothrombin time prolonged	16	5	5	11	11		
Prothrombin time ratio increased	2			2	2		
Prothrombin time shortened	8	1	1	7	7		
Psoriasis area severity index decreased	1			1	1		
Pulmonary arterial pressure abnormal	1	1	1				

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System Organ Class

Investigations

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Pulmonary arterial pressure increased	7	5	5	2	2		
Pulmonary function test	1	1	1				
Pulmonary function test abnormal	2	1	1	1	1		
Pulmonary function test decreased	2			2	2		
Pulse abnormal	87	41	41	45	46		
Pulse absent	25	20	20	5	5		
Pulse pressure decreased	3	2	2	1	1		
Pulse pressure increased	4			4	4		
Pulse volume decreased	8	2	2	6	6		
Pulse waveform abnormal	1			1	1		
Pupillary light reflex tests abnormal	1	1	1				
Quality of life decreased	28	16	16	12	12		
Radial pulse abnormal	9	7	7	2	2		
Radial pulse increased	1	1	1				
Radioisotope uptake increased	1	1	1				
Red blood cell count abnormal	3	1	1	2	2		
Red blood cell count decreased	41	10	10	31	31		
Red blood cell count increased	13			13	13		
Red blood cell sedimentation rate abnormal	4	3	3	1	1		
Red blood cell sedimentation rate increased	65	23	23	42	42		
Red blood cells urine	1	1	1				
Red blood cells urine positive	8	4	4	4	4		
Red cell distribution width decreased	3			3	3		
Red cell distribution width increased	8	1	1	7	7		
Renal function test abnormal	7	1	1	6	6		
Respiratory rate	2	1	1	1	1		
Respiratory rate decreased	42	21	21	21	21		

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System Organ Class

Investigations

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Respiratory rate increased	170	97	97	72	73		
Reticulocyte count decreased	3	2	2	1	1		
Reticulocyte count increased	1			1	1		
Retinogram abnormal	1	1	1				
Rheumatoid factor	2	1	1	1	1		
Rheumatoid factor increased	7	6	6	1	1		
Rheumatoid factor positive	7	4	4	3	3		
Rinne tuning fork test abnormal	1			1	1		
Romberg test positive	1			1	1		
Salmonella test positive	1	1	1				
SARS-CoV-1 test positive	3			3	3		
SARS-CoV-2 antibody test	5	1	1	4	4		
SARS-CoV-2 antibody test negative	149	22	22	127	127		
SARS-CoV-2 antibody test positive	93	9	9	84	84		
SARS-CoV-2 RNA	1			1	1		
SARS-CoV-2 test	6	1	1	5	5		
SARS-CoV-2 test false positive	12	2	2	10	10		
SARS-CoV-2 test negative	30	10	10	20	20		
SARS-CoV-2 test positive	674	471	473	199	201	6	6
Scan abdomen abnormal	1	1	1				
Scan abnormal	1	1	1				
Semen volume abnormal	1			1	1		
Sensory level abnormal	10	3	3	7	7		
Seroconversion test negative	4	2	2	2	2		
Serology negative	2			2	2		
Serratia test positive	1	1	1				
Serum ferritin abnormal	2	2	2				

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System Organ Class

Investigations

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Serum ferritin decreased	7	5	5	2	2		
Serum ferritin increased	15	6	6	9	9		
Shift to the left	2	1	1	1	1		
Sigmoidoscopy abnormal	1	1	1				
Sinus rhythm	5	3	3	2	2		
Skin temperature	15	6	6	9	9		
Skin test positive	1			1	1		
Skin turgor decreased	2	2	2				
Skull X-ray	1	1	1				
Sputum abnormal	6	4	4	2	2		
Sputum normal	1			1	1		
Stenotrophomonas test positive	1	1	1				
Streptococcus test negative	1			1	1		
Streptococcus test positive	4	3	3	1	1		
Stroke volume decreased	1	1	1				
Swollen joint count increased	1	1	1				
Synovial fluid analysis abnormal	1	1	1				
Synovial fluid white blood cells positive	1	1	1				
Systemic lupus erythematosus disease activity index decrea	1			1	1		
Temperature difference of extremities	6	4	4	2	2		
Temperature perception test abnormal	2	1	1	1	1		
Temperature perception test increased	2	1	1	1	1		
Thyroglobulin increased	1	1	1				
Thyroid function test abnormal	10	2	2	8	8		
Thyroid hormones increased	6	2	2	4	4		
Thyroxine decreased	2			2	2		
Thyroxine free decreased	2	1	1	1	1		

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System Organ Class

Investigations

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Thyroxine free increased	4	2	2	2	2		
Thyroxine increased	1			1	1		
Tidal volume decreased	1	1	1				
T-lymphocyte count decreased	1	1	1				
T-lymphocyte count increased	1			1	1		
Total cholesterol/HDL ratio decreased	1			1	1		
Total lung capacity decreased	3	1	1	2	2		
Toxoplasma serology positive	1			1	1		
Transaminases decreased	1	1	1				
Transaminases increased	49	26	26	23	23		
Transferrin abnormal	1	1	1				
Transferrin decreased	1			1	1		
Transferrin increased	1			1	1		
Treponema test positive	1			1	1		
Tri-iodothyronine	1			1	1		
Tri-iodothyronine decreased	4	3	3	1	1		
Tri-iodothyronine free decreased	1			1	1		
Tri-iodothyronine free increased	1			1	1		
Tri-iodothyronine increased	2	1	1	1	1		
Troponin	4	2	2	2	2		
Troponin abnormal	5	4	4	1	1		
Troponin I decreased	1			1	1		
Troponin I increased	12	9	9	3	3		
Troponin increased	123	97	97	26	26		
Troponin T increased	14	13	13	1	1		
Tryptase decreased	2			2	2		
Tryptase increased	2	1	1	1	1		

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System Organ Class

Investigations

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Tuberculin test	1			1	1		
Tuberculin test positive	2	1	1	1	1		
Tumour marker abnormal	1	1	1				
Tumour marker increased	5	2	2	3	3		
Ultrasound breast abnormal	1	1	1				
Ultrasound Doppler abnormal	1			1	1		
Ultrasound foetal abnormal	1	1	1				
Ultrasound liver abnormal	1			1	1		
Ultrasound scan abnormal	2	1	1	1	1		
Urea urine	1			1	1		
Urinary occult blood	1	1	1				
Urinary occult blood positive	4	3	3	1	1		
Urinary sediment abnormal	1			1	1		
Urinary sediment present	2	1	1	1	1		
Urine albumin/creatinine ratio increased	1	1	1				
Urine analysis abnormal	20	5	5	15	15		
Urine ketone body present	4	2	2	2	2		
Urine leukocyte esterase positive	2			2	2		
Urine output	6	3	3	3	3		
Urine output decreased	36	14	14	22	22		
Urine output increased	10	3	3	7	7		
Urine porphobilinogen increased	1	1	1				
Urine sodium increased	1	1	1				
Urobilinogen urine increased	1			1	1		
Varicella virus test positive	3	3	3				
Vascular test abnormal	2	1	1	1	1		
Venogram abnormal	1	1	1				

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System Organ Class

Investigations

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Venous bruit	1			1	1		
Venous oxygen saturation decreased	2	2	2				
Venous pressure	1			1	1		
Vestibular function test abnormal	1	1	1				
Vibration test abnormal	1	1	1				
Viral test	2	2	2				
Viral test positive	3	1	1	2	2		
Vital capacity	1	1	1				
Vital functions abnormal	3	2	2	1	1		
Vitamin B12	1			1	1		
Vitamin B12 decreased	7	4	4	3	3		
Vitamin B12 increased	4	1	1	3	3		
Vitamin B6 decreased	1			1	1		
Vitamin D	1	1	1				
Vitamin D decreased	13	1	1	12	12		
Volume blood	1			1	1		
Volume blood decreased	1	1	1				
Von Willebrand's factor activity decreased	1	1	1				
Walking distance test abnormal	1			1	1		
Weber tuning fork test abnormal	1			1	1		
Weight	1			1	1		
Weight abnormal	3	1	1	2	2		
Weight decreased	445	163	163	282	282	1	1
Weight increased	105	21	21	84	84		
White blood cell count	1			1	1		
White blood cell count abnormal	4	2	2	2	2		
White blood cell count decreased	104	38	39	65	65	2	2

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System Organ Class

Investigations

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
White blood cell count increased	192	66	67	125	125		
White blood cells urine	5	3	3	2	2		
White blood cells urine positive	10	3	3	7	7		
X-ray abnormal	3	1	1	2	2		
Total:	22417	8661	8672	13723	13745	43	43

System Organ Class

Metabolism and nutrition disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Abnormal loss of weight	14	11	11	3	3		
Abnormal weight gain	6	4	4	2	2		
Acetonaemia	3	1	1	2	2		
Acidosis	10	9	9	1	1		
Acidosis hyperchloraemic	1	1	1				
Adult failure to thrive	2	2	2				
Alcohol intolerance	6	4	4	2	2		
Alkalosis	2	2	2				
Appetite disorder	38	10	10	28	28		
Body fat disorder	1			1	1		
Cachexia	18	18	18				
Cell death	5	5	5				
Chvostek's sign	1			1	1		
Dairy intolerance	2	2	2				
Decreased appetite	4081	1152	1153	2927	2928	9	9
Decreased insulin requirement	2	1	1	1	1		
Dehydration	581	291	292	288	289		

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System Organ Class

Metabolism and nutrition disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Diabetes mellitus	104	97	97	7	7	1	1
Diabetes mellitus inadequate control	50	50	50				
Diabetic complication	5	5	5				
Diabetic ketoacidosis	24	23	23	1	1		
Diabetic ketosis	3	3	3				
Diabetic metabolic decompensation	9	9	9				
Diet refusal	10	9	9	1	1		
Dyslipidaemia	10	2	2	8	8		
Eating disorder symptom	11	3	3	8	8		
Electrolyte depletion	1			1	1		
Electrolyte imbalance	16	11	11	5	5		
Failure to thrive	2	2	2				
Feeding disorder	287	100	100	187	187		
Feeding intolerance	1			1	1		
Fluid imbalance	5	2	2	3	3		
Fluid intake reduced	28	16	16	12	12		
Fluid overload	13	6	6	7	7		
Fluid retention	77	39	39	38	38		
Folate deficiency	5	1	1	4	4		
Food aversion	20	9	9	11	11		
Food craving	14	6	6	8	8		
Food intolerance	16	7	7	9	9		
Food refusal	19	12	12	7	7		
Glucose tolerance impaired	5	3	3	2	2		
Gluten sensitivity	6	2	2	4	4		
Glycopenia	1			1	1		
Gout	155	72	72	83	83		

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System Organ Class

Metabolism and nutrition disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Haemochromatosis	1			1	1		
Histamine intolerance	6	2	2	4	4		
Hypercalcaemia	10	9	9	1	1		
Hyperchloraemia	1	1	1				
Hypercholesterolaemia	9	4	4	5	5		
Hypercreatininaemia	1	1	1				
Hyperferritinaemia	5	3	3	2	2		
Hyperglycaemia	219	128	128	91	91	1	1
Hyperglycaemic hyperosmolar nonketotic syndrome	1	1	1				
Hyperhomocysteinaemia	2	1	1	1	1		
Hyperkalaemia	28	27	27	1	1		
Hyperlactacidaemia	6	6	6				
Hyperlipidaemia	7	3	3	4	4		
Hypermetabolism	3	2	2	1	1		
Hypernatraemia	24	19	19	5	5		
Hyperphagia	8	3	3	5	5		
Hypertriglyceridaemia	3	2	2	1	1		
Hyperuricaemia	5	1	1	4	4		
Hypervitaminosis B12	1	1	1				
Hypervolaemia	1	1	1				
Hypoalbuminaemia	8	5	5	3	3		
Hypocalcaemia	13	10	10	3	3		
Hypoglycaemia	241	123	123	117	118		
Hypokalaemia	72	72	72				
Hypokalaemic syndrome	3	2	2	1	1		
Hypomagnesaemia	3	2	2	1	1		
Hyponatraemia	54	33	33	21	21	1	1

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System Organ Class

Metabolism and nutrition disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Hyponatraemic syndrome	2	1	1	1	1		
Hypophagia	75	49	49	26	26		
Hypophosphataemia	3	1	1	2	2		
Hypoproteinaemia	1			1	1		
Hypovitaminosis	5	2	2	3	3		
Hypovolaemia	3	3	3				
Impaired fasting glucose	3	1	1	2	2		
Increased appetite	40	5	5	35	35		
Increased insulin requirement	7	4	4	3	3		
Insulin-requiring type 2 diabetes mellitus	1	1	1				
Insulin resistance	13	8	8	5	5		
Insulin resistant diabetes	2	2	2				
Iron deficiency	14	5	5	9	9		
Iron overload	1			1	1		
Ketoacidosis	10	10	10				
Lack of satiety	1			1	1		
Lactic acidosis	12	11	11	1	1		
Lactose intolerance	5	1	1	4	4		
Latent autoimmune diabetes in adults	2	2	2				
Lipid metabolism disorder	1			1	1		
Malnutrition	13	7	7	6	6		
Marasmus	12	12	12				
Metabolic acidosis	26	23	23	3	3		
Metabolic alkalosis	1			1	1		
Metabolic disorder	5	3	3	2	2		
Metabolic syndrome	1	1	1				
Mineral metabolism disorder	1	1	1				

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System Organ Class

Metabolism and nutrition disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Obesity	4			4	4		
Oligodipsia	3	1	1	2	2		
Overfeeding of infant	1			1	1		
Overweight	11	2	2	9	9		
Polydipsia	51	13	13	38	38		
Poor feeding infant	7	1	1	6	6		
Postprandial hypoglycaemia	1	1	1				
Salt craving	3	1	1	2	2		
Shock hypoglycaemic	1	1	1				
Starvation	4	4	4				
Tetany	23	13	14	9	9		
Type 1 diabetes mellitus	22	21	21	1	1		
Type 2 diabetes mellitus	15	15	15				
Underweight	4	2	2	2	2		
Vitamin B12 deficiency	5	4	4	1	1		
Vitamin B complex deficiency	1			1	1		
Vitamin D deficiency	18	8	8	10	10		
Weight fluctuation	12			12	12		
Weight loss poor	2	1	1	1	1		
Total:	6853	2705	2708	4142	4145	12	12

System Organ Class

Musculoskeletal and connective tissue disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Amplified musculoskeletal pain syndrome	1			1	1		
Amyotrophy	2	2	2				

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System Organ Class

Musculoskeletal and connective tissue disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Aneurysmal bone cyst	1			1	1		
Ankylosing spondylitis	26	26	26				
Antisynthetase syndrome	2	1	1	1	1		
Arthralgia	35342	5941	5942	29385	29400	71	71
Arthritis	568	224	224	344	344		
Arthritis allergic	1	1	1				
Arthritis enteropathic	1	1	1				
Arthritis reactive	51	50	51			1	1
Arthropathy	146	31	31	115	115		
Autoimmune arthritis	4	4	4				
Axillary mass	351	97	97	253	254		
Back disorder	47	5	5	42	42		
Back pain	5204	1450	1450	3752	3754	11	11
Bone deformity	1			1	1		
Bone development abnormal	1			1	1		
Bone disorder	30	3	3	27	27		
Bone lesion	2			2	2		
Bone pain	1586	331	331	1254	1255	3	3
Bone swelling	39	10	10	29	29		
Bursa disorder	3	1	1	2	2		
Bursal fluid accumulation	1			1	1		
Bursal haematoma	2	2	2				
Bursitis	109	53	53	56	56	1	1
Calcification of muscle	1			1	1		
Camptocormia	1			1	1		
Cervical spinal stenosis	5	5	5				
Chondritis	2	1	1	1	1		

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System Organ Class

Musculoskeletal and connective tissue disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Chondrocalcinosis	3	2	2	1	1		
Chondrocalcinosis pyrophosphate	2	2	2				
Chondromalacia	1	1	1				
Coccydynia	19	3	3	16	16		
Collagen disorder	1	1	1				
Connective tissue disorder	4	3	3	1	1		
Connective tissue inflammation	1			1	1		
Costochondritis	52	31	31	21	21		
CREST syndrome	1	1	1				
Crystal arthropathy	1	1	1				
Dactylitis	2	1	1	1	1		
Decreased nasolabial fold	3	1	1	2	2		
Degenerative bone disease	2			2	2		
Drooping shoulder syndrome	1			1	1		
Dupuytren's contracture	2	2	2				
Enthesopathy	10	7	7	3	3		
Eosinophilic fasciitis	1	1	1				
Epiphyses premature fusion	1	1	1				
Exostosis	1			1	1	1	1
Extremity contracture	10	1	1	9	9		
Facet joint syndrome	2			2	2		
Facial asymmetry	32	18	18	14	14		
Fasciitis	7	4	4	3	3		
Fibromyalgia	136	60	60	76	76	1	1
Finger deformity	12	4	4	8	8		
Fistula	3	1	1	2	2		
Flank pain	115	39	39	75	76		

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System Organ Class

Musculoskeletal and connective tissue disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Fluctuance	1			1	1		
Foot deformity	13	1	1	12	12		
Fracture pain	1	1	1				
Gouty arthritis	2			2	2		
Gouty tophus	1	1	1				
Groin pain	199	78	78	121	121	2	2
Growing pains	2			2	2		
Growth failure	1			1	1		
Haemarthrosis	20	19	19	1	1		
Haematoma muscle	12	9	9	3	3		
Hand deformity	9	5	5	4	4		
Head deformity	2	1	1	1	1		
Hypermobility syndrome	1	1	1				
Immobilisation syndrome	3	1	1	2	2		
Immune-mediated arthritis	1	1	1				
Immunoglobulin G4 related disease	1	1	1				
Inguinal mass	1	1	1				
Intervertebral disc annular tear	1			1	1		
Intervertebral disc compression	2	2	2				
Intervertebral disc degeneration	5	1	1	4	4		
Intervertebral disc disorder	5			5	5		
Intervertebral disc protrusion	27	12	12	15	15	1	1
Jaw clicking	11	3	3	8	8		
Jaw cyst	1			1	1		
Jaw disorder	31	7	7	24	24	1	1
Joint adhesion	1			1	1		
Joint ankylosis	11	2	2	9	9		

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System Organ Class

Musculoskeletal and connective tissue disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Joint contracture	4			4	4		
Joint deposit	1	1	1				
Joint destruction	1	1	1				
Joint effusion	57	24	24	33	33		
Joint hyperextension	1			1	1		
Joint instability	11	7	7	4	4		
Joint laxity	3	3	3				
Joint lock	42	13	13	29	29		
Joint microhaemorrhage	2	2	2				
Joint noise	32	15	15	17	17		
Joint range of motion decreased	438	225	225	212	213	1	1
Joint space narrowing	1			1	1		
Joint stiffness	388	171	171	217	217		
Joint swelling	961	358	358	602	603		
Joint vibration	1	1	1				
Joint warmth	30	12	12	18	18		
Knee deformity	2			2	2		
Kyphoscoliosis	1			1	1		
Kyphosis	1	1	1				
Ligament disorder	4	3	3	1	1		
Ligamentitis	2	2	2				
Ligament laxity	1			1	1		
Ligament pain	4	1	1	3	3		
Limb deformity	8	3	3	5	5		
Limb discomfort	2883	675	678	2201	2205	15	15
Limb mass	78	25	25	53	53		
Loose body in joint	2	1	1	1	1		

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System Organ Class

Musculoskeletal and connective tissue disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Lordosis	1	1	1				
Lumbar spinal stenosis	1			1	1		
Lupus-like syndrome	3	2	2	1	1		
Lupus myositis	1	1	1				
Mandibular mass	2			2	2		
Mastication disorder	42	17	17	25	25		
Masticatory pain	1			1	1		
Medial tibial stress syndrome	3	3	3				
Metatarsalgia	1			1	1		
Mixed connective tissue disease	2	2	2				
Mobility decreased	880	330	330	549	550	2	2
Morphoea	2	1	1	1	1		
Muscle atrophy	27	13	13	14	14		
Muscle contracture	77	15	15	62	62	1	1
Muscle discomfort	65	7	7	58	58		
Muscle disorder	63	16	16	47	47		
Muscle fatigue	350	158	158	192	192	1	1
Muscle haemorrhage	4	4	4				
Muscle hypertrophy	2	2	2				
Muscle mass	7	2	2	5	5		
Muscle oedema	9	3	3	6	6		
Muscle rigidity	105	38	38	67	67	1	1
Muscle spasms	2062	682	682	1377	1380	4	4
Muscle swelling	67	17	17	50	50		
Muscle tightness	411	98	99	310	312	1	1
Muscle twitching	549	161	161	388	388		
Muscular weakness	2468	1058	1059	1408	1409	2	2

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System Organ Class

Musculoskeletal and connective tissue disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Musculoskeletal chest pain	443	162	162	278	281		
Musculoskeletal deformity	1	1	1				
Musculoskeletal discomfort	392	89	89	302	303		
Musculoskeletal disorder	119	54	54	64	65		
Musculoskeletal pain	1663	161	161	1502	1502	1	1
Musculoskeletal stiffness	2504	834	834	1669	1670	5	5
Myalgia	49287	7007	7011	42260	42276	96	96
Myalgia intercostal	14	4	4	10	10		
Myofascial pain syndrome	8	4	4	4	4		
Myofascial spasm	2	1	1	1	1		
Myofascitis	3	2	2	1	1		
Myokymia	10	2	2	8	8		
Myopathy	16	8	8	8	8		
Myosclerosis	8	8	8				
Myositis	77	42	42	35	35	1	1
Neck deformity	2			2	2		
Neck mass	78	14	14	64	64		
Neck pain	3859	1196	1196	2659	2663	4	4
Neuropathic muscular atrophy	1	1	1				
Nodal osteoarthritis	1			1	1		
Nose deformity	1			1	1		
Nuchal rigidity	102	25	25	77	77		
Oligoarthritis	3	3	3				
Osteitis	11	2	2	9	9		
Osteoarthritis	77	34	34	43	43		
Osteoarthropathy	6			6	6		
Osteochondritis	2			2	2		

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System Organ Class

Musculoskeletal and connective tissue disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Osteolysis	1			1	1		
Osteonecrosis of jaw	2	2	2				
Osteopenia	4	1	1	3	3		
Osteoporosis	10	2	2	8	8		
Osteoporotic fracture	1	1	1				
Pain in extremity	28240	5816	5822	22390	22418	104	104
Pain in jaw	603	206	206	397	397	1	1
Palindromic rheumatism	3	3	3				
Patellofemoral pain syndrome	2	1	1	1	1		
Pathological fracture	1	1	1				
Periarthritis	108	69	69	39	39	2	2
Plantar fasciitis	12	5	5	7	7		
Polyarthritis	44	42	42	2	2		
Polychondritis	4	4	4				
Polymyalgia rheumatica	93	87	87	6	6		
Polymyositis	7	7	7				
Posture abnormal	15	7	7	8	8		
Psoriatic arthropathy	32	31	32			1	1
Purple glove syndrome	1	1	1				
Reynold's syndrome	1	1	1				
Rhabdomyolysis	55	55	55				
Rheumatic disorder	28	11	11	17	17		
Rheumatic fever	2	2	2				
Rheumatoid arthritis	239	234	234	5	5	10	10
Rotator cuff syndrome	34	21	21	13	13	1	1
Sacroiliitis	10	5	5	5	5		
SAPHO syndrome	1	1	1				

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System Organ Class

Musculoskeletal and connective tissue disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Scleroderma	3	3	3				
Scoliosis	4	2	2	2	2		
Seronegative arthritis	4	4	4				
Sinus tarsi syndrome	1			1	1		
Sjogren's syndrome	23	23	23				
SLE arthritis	2	2	2				
Snapping hip syndrome	1			1	1		
Soft tissue atrophy	1	1	1				
Soft tissue disorder	4	1	1	3	3		
Soft tissue haemorrhage	1			1	1		
Soft tissue swelling	59	4	4	55	55		
Somatic dysfunction	1	1	1				
Spinal disorder	15	7	7	8	8		
Spinal osteoarthritis	16	7	7	9	9		
Spinal pain	293	75	75	218	218		
Spinal stenosis	6	2	2	4	4		
Spondylitis	13	8	8	5	5		
Spondyloarthropathy	1			1	1		
Still's disease	2	2	2			1	1
Symphysiolysis	1	1	1				
Synovial cyst	51	23	23	28	28		
Synovial disorder	1			1	1		
Synovitis	21	11	11	10	10		
Systemic lupus erythematosus	50	50	50			2	2
Systemic scleroderma	1	1	1				
Temporomandibular joint syndrome	26	8	8	18	18		
Tendon discomfort	3			3	3		

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System Organ Class

Musculoskeletal and connective tissue disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Tendon disorder	21	8	8	13	13		
Tendonitis	103	44	44	59	59		
Tendon pain	59	21	21	38	38		
Tenosynovitis	26	9	9	17	17		
Tenosynovitis stenosans	4	3	3	1	1		
Toe walking	1			1	1		
Torticollis	54	7	7	47	47		
Trigger finger	25	6	6	19	19		
Trismus	68	24	24	44	44		
Undifferentiated connective tissue disease	1	1	1				
Vertebral lesion	2	2	2				
Vertebral wedging	1	1	1				
Weight bearing difficulty	34	16	16	18	18		
Winged scapula	2	1	1	1	1		
Total:	145732	29395	29413	116232	116319	350	350

System Organ Class

Neoplasms benign, malignant and unspecified (incl cyst

Preferred Term	*Total # of Spontaneous AE*	Spontaneous			
		Serious		Nonserious	
		I	C	I	C
Acoustic neuroma	4	4	4		
Acrochordon	2	1	1	1	1
Acute leukaemia	5	5	5		
Acute lymphocytic leukaemia	1	1	1		
Acute monocytic leukaemia	1	1	1		
Acute myeloid leukaemia	8	7	7	1	1
Adenocarcinoma pancreas	1	1	1		

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System Organ Class

Neoplasms benign, malignant and unspecified (incl cyst

Preferred Term	*Total # of Spontaneous AE*	Spontaneous			
		Serious		Nonserious	
		I	C	I	C
Adenoma benign	2	1	1	1	1
Angiomyolipoma	1	1	1		
Anogenital warts	1			1	1
Basal cell carcinoma	4	4	4		
B-cell lymphoma	3	3	3		
B-cell type acute leukaemia	2	2	2		
Benign breast neoplasm	1			1	1
Benign hydatidiform mole	1	1	1		
Benign lymph node neoplasm	1	1	1		
Benign neoplasm	1			1	1
Bile duct cancer	1	1	1		
Bladder cancer	1	1	1		
Bladder neoplasm	1	1	1		
Blast cell crisis	1	1	1		
Bone neoplasm	6	3	3	3	3
Brain cancer metastatic	1	1	1		
Brain neoplasm	9	9	9		
Breast cancer	27	26	26	1	1
Breast cancer female	2	2	2		
Breast cancer metastatic	1	1	1		
Breast cancer recurrent	1	1	1		
Breast cancer stage I	1	1	1		
Breast cancer stage III	1	1	1		
Bronchial neoplasm	1	1	1		
Cardiac neoplasm unspecified	1	1	1		
Castleman's disease	1	1	1		
Chronic leukaemia	1	1	1		

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System Organ Class

Neoplasms benign, malignant and unspecified (incl cyst

Preferred Term	*Total # of Spontaneous AE*	Spontaneous			
		Serious		Nonserious	
		I	C	I	C
Chronic lymphocytic leukaemia	12	12	12		
Chronic lymphocytic leukaemia recurrent	1	1	1		
Chronic lymphocytic leukaemia stage 0	1	1	1		
Chronic myeloid leukaemia recurrent	1	1	1		
Chronic myelomonocytic leukaemia	1			1	1
Colon cancer	3	3	3		
Colon neoplasm	2	2	2		
Cranial nerve neoplasm benign	1	1	1		
Diffuse large B-cell lymphoma	1	1	1		
Ear neoplasm	1			1	1
Endometrial cancer	1	1	1		
Essential thrombocythaemia	1	1	1		
Eyelid tumour	1			1	1
Fallopian tube neoplasm	1	1	1		
Fibroma	2			2	2
Fibrous histiocytoma	1			1	1
Follicular lymphoma	2	2	2		
Gastric cancer	1	1	1		
Gastrointestinal carcinoma	2	2	2		
Good syndrome	1	1	1		
Haemangioma	4	1	1	3	3
Haemangioma of liver	1			1	1
Haemangioma of skin	5	2	2	3	3
Hepatic cancer	1	1	1		
Hepatocellular carcinoma	1	1	1		
Histiocytosis	1	1	1		
Hodgkin's disease	2	2	2		

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System Organ Class

Neoplasms benign, malignant and unspecified (incl cyst

Preferred Term	*Total # of Spontaneous AE*	Spontaneous			
		Serious		Nonserious	
		I	C	I	C
Hypergammaglobulinaemia benign monoclonal	1	1	1		
Inflammatory carcinoma of the breast	1	1	1		
Invasive ductal breast carcinoma	2	2	2		
Kaposi's sarcoma AIDS related	1	1	1		
Large intestine benign neoplasm	1			1	1
Leukaemia	11	11	11		
Leukaemia recurrent	1	1	1		
Lip and/or oral cavity cancer recurrent	1	1	1		
Lipoma	11	4	4	7	7
Lung cancer metastatic	3	3	3		
Lung carcinoma cell type unspecified recurrent	1	1	1		
Lung carcinoma cell type unspecified stage I	1	1	1		
Lung neoplasm	1	1	1		
Lung neoplasm malignant	10	9	9	1	1
Lymphangioma	1	1	1		
Lymphoma	33	32	32	1	1
Lymphoproliferative disorder	2	2	2		
Malignant lymphoid neoplasm	1	1	1		
Malignant melanoma	2	2	2		
Malignant neoplasm of eye	1	1	1		
Malignant peritoneal neoplasm	2	2	2		
Malignant pleural effusion	1	1	1		
Mantle cell lymphoma recurrent	1	1	1		
Melanocytic naevus	6	1	1	5	5
Melanoma recurrent	2	2	2		
Meningioma	4	4	4		
Metastases to bone	1	1	1		

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System Organ Class

Neoplasms benign, malignant and unspecified (incl cyst

Preferred Term	*Total # of Spontaneous AE*	Spontaneous			
		Serious		Nonserious	
		I	C	I	C
Metastases to breast	1	1	1		
Metastases to central nervous system	2	2	2		
Metastases to lung	2	2	2		
Metastases to lymph nodes	9	9	9		
Metastases to meninges	2	2	2		
Metastases to peritoneum	2	2	2		
Metastasis	2	2	2		
Metastatic neoplasm	1	1	1		
Monoclonal gammopathy	5	3	3	2	2
Myelodysplastic syndrome	8	8	8		
Myelofibrosis	1	1	1		
Myeloid leukaemia	1	1	1		
Myeloproliferative neoplasm	1			1	1
Neoplasm	32	13	13	19	19
Neoplasm malignant	30	28	28	2	2
Neoplasm progression	17	10	10	7	7
Neoplasm recurrence	5	3	3	2	2
Neoplasm skin	9	2	2	7	7
Neoplasm swelling	1			1	1
Neuroendocrine carcinoma of the skin	1	1	1		
Neuroma	1			1	1
Nodular fasciitis	1			1	1
Non-Hodgkin's lymphoma	6	6	6		
Oligodendroglioma	1	1	1		
Oncologic complication	1			1	1
Ovarian cancer	2	2	2		
Ovarian neoplasm	1	1	1		

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System Organ Class

Neoplasms benign, malignant and unspecified (incl cyst

Preferred Term	*Total # of Spontaneous AE*	Spontaneous			
		Serious		Nonserious	
		I	C	I	C
Pancreatic carcinoma	4	4	4		
Pancreatic carcinoma metastatic	1	1	1		
Papillary thyroid cancer	1	1	1		
Phaeochromocytoma	1	1	1		
Pituitary tumour	1	1	1		
Pituitary tumour benign	4	3	3	1	1
Plasma cell leukaemia	1	1	1		
Plasma cell myeloma	6	6	6		
POEMS syndrome	2	2	2		
Polycythaemia vera	1	1	1		
Primary gastrointestinal follicular lymphoma	1	1	1		
Prostate cancer	9	9	9		
Renal cancer	2	2	2		
Renal cancer metastatic	1	1	1		
Renal neoplasm	2	2	2		
Rosai-Dorfman syndrome	1	1	1		
Salivary gland adenoma	1	1	1		
Salivary gland neoplasm	1	1	1		
Sarcoma	1	1	1		
Schwannoma	1	1	1		
Second primary malignancy	1	1	1		
Skin cancer	5	5	5		
Skin papilloma	9	2	2	7	7
Squamous cell carcinoma	3	3	3		
Squamous cell carcinoma of skin	1	1	1		
T-cell lymphoma	1	1	1		
TEMPI syndrome	1	1	1		

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System Organ Class

Neoplasms benign, malignant and unspecified (incl cyst

Preferred Term	*Total # of Spontaneous AE*	Spontaneous			
		Serious		Nonserious	
		I	C	I	C
Testicular neoplasm	1	1	1		
Thymoma	1	1	1		
Thyroid cancer	3	3	3		
Thyroid neoplasm	1	1	1		
Triple negative breast cancer	2	2	2		
Tumour pain	3	3	3		
Tumour perforation	1	1	1		
Tumour pseudoprogression	1	1	1		
Tumour thrombosis	1	1	1		
Uterine leiomyoma	12	7	7	5	5
Yolk sac tumour site unspecified	1	1	1		
Total:	486	391	391	95	95

System Organ Class

Nervous system disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Acoustic neuritis	3	2	2	1	1		
Acrodynia	2			2	2		
Action tremor	1			1	1		
Acute disseminated encephalomyelitis	22	22	22				
Acute motor axonal neuropathy	2	2	2				
Acute polyneuropathy	3	3	3				
Adrenergic syndrome	1			1	1		
Advanced sleep phase	1			1	1		
Ageusia	1124	244	244	878	880	6	6
Agnosia	2	1	1	1	1		

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System Organ Class

Nervous system disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Akathisia	12	4	4	8	8		
Akinesia	5	4	4	1	1		
Alcoholic seizure	1	1	1				
Alexia	3	1	1	2	2		
Allodynia	38	9	9	29	29		
Altered pitch perception	1			1	1		
Altered state of consciousness	192	184	184	8	8	1	1
Amnesia	339	181	181	158	158		
Amnestic disorder	6	6	6				
Amputation stump pain	1			1	1		
Amyotrophic lateral sclerosis	1	1	1				
Anaesthesia	133	9	9	124	124		
Anaesthesia dolorosa	1	1	1				
Anosmia	913	168	168	745	745	5	5
Anosognosia	1	1	1				
Anterograde amnesia	5	5	5				
Anticholinergic syndrome	1	1	1				
Apallic syndrome	6	6	6				
Aphasia	405	285	285	120	120	4	4
Apraxia	10	5	5	5	5		
Arachnoid cyst	2	2	2				
Areflexia	22	19	19	3	3		
Asterixis	1	1	1				
Ataxia	67	44	44	23	23		
Atonic seizures	5	4	4	1	1		
Aura	43	15	15	28	28		
Autoimmune demyelinating disease	1	1	1				

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System Organ Class

Nervous system disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Autoimmune neuropathy	1	1	1				
Autonomic nervous system imbalance	32	24	24	8	8		
Autonomic neuropathy	3	3	3				
Autonomic seizure	1	1	1				
Axonal neuropathy	5	4	4	1	1		
Balance disorder	1168	496	497	670	671	6	6
Ballismus	1	1	1				
Band sensation	28	4	4	24	24	1	1
Basal ganglia haematoma	1	1	1				
Basal ganglia haemorrhage	6	6	6				
Basal ganglia infarction	5	5	5				
Basal ganglia stroke	5	5	5				
Basilar artery occlusion	5	5	5				
Basilar artery thrombosis	14	13	13	1	1		
Basilar migraine	1	1	1				
Bell's palsy	1029	1021	1023	6	6	2	2
Bickerstaff's encephalitis	1	1	1				
Brachial plexopathy	4	2	2	2	2		
Bradykinesia	50	17	17	33	33	1	1
Brain compression	3	3	3				
Brain hypoxia	4	4	4				
Brain injury	24	22	22	2	2		
Brain oedema	40	37	37	3	3		
Brain stem haemorrhage	9	9	9				
Brain stem infarction	16	15	15	1	1		
Brain stem ischaemia	4	4	4				
Brain stem stroke	12	12	12				

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System Organ Class

Nervous system disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Brain stem syndrome	7	7	7				
Brain stem thrombosis	1	1	1				
Brown-Sequard syndrome	1	1	1				
Bulbar palsy	2	2	2				
Burning feet syndrome	10	5	5	5	5		
Burning sensation	1621	458	458	1161	1163	1	1
Burning sensation mucosal	14	1	1	13	13		
Carotid arteriosclerosis	10	6	6	4	4		
Carotid artery disease	1	1	1				
Carotid artery dissection	10	10	10				
Carotid artery occlusion	18	18	18				
Carotid artery stenosis	12	12	12				
Carotid artery thrombosis	15	15	15				
Carpal tunnel syndrome	42	23	23	19	19		
Cataplexy	5	5	5				
Cauda equina syndrome	1	1	1				
Central nervous system inflammation	2	2	2				
Central nervous system lesion	11	8	8	3	3		
Central nervous system vasculitis	5	5	5				
Central pain syndrome	8	1	1	7	7		
Cerebellar artery thrombosis	1	1	1				
Cerebellar ataxia	6	3	3	3	3		
Cerebellar atrophy	1	1	1				
Cerebellar embolism	1	1	1				
Cerebellar haematoma	2	2	2				
Cerebellar haemorrhage	15	15	15				
Cerebellar infarction	17	17	17				

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System Organ Class

Nervous system disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Cerebellar ischaemia	3	3	3				
Cerebellar stroke	17	17	17				
Cerebellar syndrome	10	10	10				
Cerebral amyloid angiopathy	4	4	4				
Cerebral arteriosclerosis	4	3	3	1	1		
Cerebral artery embolism	20	19	19	1	1		
Cerebral artery occlusion	15	15	15				
Cerebral artery stenosis	4	4	4				
Cerebral artery thrombosis	16	16	16				
Cerebral atrophy	11	11	11				
Cerebral congestion	3	3	3				
Cerebral cyst	1	1	1				
Cerebral disorder	35	11	11	24	24		
Cerebral haematoma	30	30	30				
Cerebral haemorrhage	310	309	309	1	1		
Cerebral infarction	401	399	399	2	2	1	1
Cerebral ischaemia	67	67	67			1	1
Cerebral mass effect	2	2	2				
Cerebral microangiopathy	1	1	1				
Cerebral microhaemorrhage	1	1	1				
Cerebral microinfarction	1	1	1				
Cerebral small vessel ischaemic disease	8	8	8				
Cerebral thrombosis	91	91	91			3	3
Cerebral vascular occlusion	1	1	1				
Cerebral vasoconstriction	1	1	1				
Cerebral venous sinus thrombosis	105	105	105			1	1
Cerebral venous thrombosis	34	34	34				

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System Organ Class

Nervous system disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Cerebral ventricular rupture	3	3	3				
Cerebrospinal fluid leakage	2	2	2				
Cerebrovascular accident	1197	1189	1190	7	7	3	3
Cerebrovascular disorder	20	19	19	1	1	1	1
Cerebrovascular insufficiency	2	2	2				
Cervical cord compression	1	1	1				
Cervical neuritis	1			1	1		
Cervical radiculopathy	26	9	9	17	17		
Cervicobrachial syndrome	41	13	13	28	28		
Cervicogenic headache	10	2	2	8	8		
Cervicogenic vertigo	1			1	1		
Cholinergic syndrome	7	7	7				
Chorea	7	6	6	1	1		
Chronic inflammatory demyelinating polyradiculoneuropathy	6	6	6				
Circadian rhythm sleep disorder	9	2	2	7	7		
Clinically isolated syndrome	1	1	1				
Clonic convulsion	11	11	11				
Clonus	19	11	11	8	8		
Clumsiness	32	11	11	21	21		
Cluster headache	154	89	89	65	65	1	1
Cognitive disorder	206	113	113	93	93	1	1
Cognitive linguistic deficit	2			2	2		
Cogwheel rigidity	1			1	1		
Cold-stimulus headache	11	6	6	5	5		
Coma	85	85	85				
Coma hepatic	2	2	2				
Complex regional pain syndrome	14	10	10	4	4		

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System Organ Class

Nervous system disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Concentric sclerosis	1	1	1				
Consciousness fluctuating	7	7	7				
Conus medullaris syndrome	1	1	1				
Convulsions local	5	5	5				
Coordination abnormal	131	78	78	53	53	1	1
Cramp-fasciculation syndrome	3	1	1	2	2		
Cranial nerve disorder	15	9	9	6	6		
Cranial nerve palsies multiple	3	3	3				
Cranial nerve paralysis	10	10	10				
Cubital tunnel syndrome	2	2	2				
Cytotoxic oedema	1	1	1				
Decerebrate posture	1	1	1				
Decreased vibratory sense	2	2	2				
Delayed ischaemic neurological deficit	1	1	1				
Dementia	74	72	72	2	2		
Dementia Alzheimer's type	18	17	17	1	1		
Dementia of the Alzheimer's type, with delirium	1	1	1				
Dementia with Lewy bodies	1	1	1				
Demyelinating polyneuropathy	10	10	10				
Demyelination	26	26	26				
Depressed level of consciousness	473	463	463	10	10	3	3
Diabetic coma	5	5	5				
Diabetic hyperosmolar coma	2	2	2				
Diabetic neuropathy	1			1	1		
Diplegia	33	32	32	1	1		
Disturbance in attention	926	353	353	573	573	4	4
Dizziness	23896	6342	6352	17511	17544	75	75

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System Organ Class

Nervous system disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Dizziness exertional	35	27	27	8	8		
Dizziness postural	620	322	323	296	297	1	1
Dreamy state	4	2	2	2	2		
Drooling	38	17	17	21	21		
Drop attacks	2	2	2				
Dropped head syndrome	2	2	2				
Dysaesthesia	255	76	76	179	179		
Dysarthria	455	308	308	146	147	8	8
Dysdiadochokinesis	1	1	1				
Dysgeusia	2508	461	462	2038	2046	4	4
Dysgraphia	29	12	12	17	17		
Dyskinesia	241	97	97	144	144		
Dyslalia	23	18	18	5	5		
Dyslexia	8	3	3	5	5		
Dysmetria	5	5	5				
Dyspraxia	8	4	4	4	4		
Dysstasia	450	209	209	241	241	1	1
Dystonia	30	30	30				
Electric shock sensation	111	31	31	80	80		
Embolic cerebellar infarction	1	1	1				
Embolic cerebral infarction	11	11	11				
Embolic stroke	39	38	38	1	1		
Encephalitis autoimmune	6	6	6				
Encephalitis post immunisation	2	2	2				
Encephalomalacia	2	2	2				
Encephalopathy	28	27	27	1	1		
Epilepsy	416	412	412	4	4	1	1

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System Organ Class

Nervous system disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Epileptic aura	3	2	2	1	1		
Epileptic encephalopathy	1	1	1				
Essential tremor	7	4	4	3	3		
Exaggerated startle response	2			2	2		
Exertional headache	8	3	3	5	5		
Extensor plantar response	5	3	3	2	2		
Extrapyramidal disorder	9	7	7	2	2		
Facial nerve disorder	30	11	11	19	19		
Facial neuralgia	60	16	16	44	44		
Facial paralysis	1221	1204	1207	14	14	3	3
Facial paresis	433	296	296	137	137	1	1
Facial spasm	59	19	19	40	40		
Febrile convulsion	108	51	51	57	57		
Fine motor skill dysfunction	31	11	11	20	20		
Focal dyscognitive seizures	5	5	5				
Foetal movement disorder	1	1	1				
Formication	180	55	55	125	125		
Freezing phenomenon	20	5	5	15	15		
Fumbling	5	2	2	3	3		
Generalised onset non-motor seizure	3	3	3				
Generalised tonic-clonic seizure	174	172	172	2	2		
Glabellar reflex abnormal	1			1	1		
Gliosis	2	1	1	1	1		
Glossopharyngeal nerve disorder	1	1	1				
Gross motor delay	2	2	2				
Guillain-Barre syndrome	223	221	221	2	2		
Haemorrhage intracranial	29	28	28	1	1		

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System Organ Class

Nervous system disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Haemorrhagic cerebral infarction	7	7	7				
Haemorrhagic stroke	69	69	69				
Haemorrhagic transformation stroke	9	9	9				
Hand-arm vibration syndrome	2	2	2				
Hand-eye coordination impaired	3	2	2	1	1		
Headache	83564	14542	14556	68950	69008	178	178
Head discomfort	969	287	288	677	681		
Head titubation	14	4	4	10	10		
Hemianaesthesia	56	54	54	2	2	1	1
Hemianopia	13	13	13				
Hemianopia heteronymous	1	1	1				
Hemianopia homonymous	10	10	10				
Hemiapraxia	1	1	1				
Hemiataxia	3	3	3				
Hemidysaesthesia	9	9	9				
Hemihyperaesthesia	6	6	6				
Hemiparaesthesia	91	85	85	6	6		
Hemiparesis	337	330	330	7	7	1	1
Hemiplegia	181	180	180	1	1		
Hemiplegic migraine	14	12	12	2	2		
Hepatic encephalopathy						1	1
Hippocampal atrophy	2	1	1	1	1		
Hippocampal sclerosis	1	1	1				
Hoffmann's sign	1			1	1		
Horner's syndrome	5	5	5				
Hydrocephalus	9	9	9				
Hyperaesthesia	399	98	98	301	301		

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System Organ Class

Nervous system disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Hypercapnic coma	1	1	1				
Hypergeusia	3	1	1	2	2		
Hyperintensity in brain deep nuclei	2	2	2				
Hyperkinesia	2			2	2		
Hyperpathia	3			3	3		
Hyperreflexia	12	8	8	4	4		
Hyperresponsive to stimuli	1	1	1				
Hypersomnia	567	190	190	377	377		
Hypertensive encephalopathy	7	7	7				
Hypertonia	24	13	13	11	11	1	1
Hypoaesthesia	6241	2061	2065	4170	4176	10	10
Hypogeusia	50	7	7	43	43		
Hypoglossal nerve disorder	1	1	1				
Hypoglossal nerve paresis	1	1	1				
Hypoglycaemic coma	2	2	2				
Hypoglycaemic seizure	1	1	1				
Hypoglycaemic unconsciousness	2	1	1	1	1		
Hypokinesia	435	118	118	317	317		
Hyporeflexia	24	15	15	9	9		
Hyporesponsive to stimuli	18	11	11	7	7		
Hyposmia	55	12	12	43	43		
Hypotonia	234	59	59	175	175		
Hypotonic-hyporesponsive episode	43	33	33	10	10		
Hypoxic-ischaemic encephalopathy	8	8	8				
Idiopathic intracranial hypertension	13	13	13				
IIIrd nerve disorder	5	5	5				
IIIrd nerve paralysis	25	25	25				

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System Organ Class

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Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
IIIrd nerve paresis	3	3	3				
Immune-mediated neuropathy	1	1	1				
Inability to crawl	1	1	1				
Incoherent	49	25	25	24	24		
Infant irritability	11	5	5	6	6		
Intellectual disability	2	2	2				
Intention tremor	3	3	3				
Intercostal neuralgia	8	2	2	6	6		
Internal capsule infarction	1	1	1				
Intracranial aneurysm	15	15	15				
Intracranial artery dissection	1	1	1				
Intracranial haematoma	1	1	1				
Intracranial hypotension	2	1	1	1	1		
Intracranial mass	1	1	1				
Intracranial pressure increased	22	22	22				
Intraventricular haemorrhage	10	10	10				
Irregular sleep phase	1			1	1		
Irregular sleep wake rhythm disorder	4			4	4		
Ischaemic cerebral infarction	56	56	56				
Ischaemic stroke	417	417	417			3	3
IVth nerve disorder	2	2	2				
IVth nerve paralysis	13	13	13				
IVth nerve paresis	1	1	1				
Lacunar infarction	23	22	22	1	1		
Lacunar stroke	11	11	11				
Language disorder	24	18	18	6	6		
Lateral medullary syndrome	3	3	3				

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System Organ Class

Nervous system disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Lateropulsion	3	2	2	1	1	1	1
Lennox-Gastaut syndrome	1	1	1				
Lethargy	2947	904	905	2042	2042	10	10
Leukoencephalopathy	9	9	9				
Lhermitte's sign	3	1	1	2	2		
Limbic encephalitis	2	2	2				
Locked-in syndrome	2	2	2				
Long thoracic nerve palsy	1			1	1		
Loss of consciousness	2080	2030	2032	48	48	5	5
Loss of proprioception	7	4	4	3	3		
Lower motor neurone lesion	2	2	2				
Lumbar radiculopathy	3			3	3		
Medication overuse headache	2	1	1	1	1		
Memory impairment	415	150	151	264	264	2	2
Meningeal disorder	6	3	3	3	3		
Meningism	13	8	8	5	5		
Meningitis noninfective	1	1	1				
Meningoradiculitis	4	4	4				
Meningorrhagia	1	1	1				
Mental impairment	164	155	155	9	9	1	1
Meralgia paraesthetica	2	2	2				
Metabolic encephalopathy	2	2	2				
Migraine	3412	1334	1334	2075	2078	11	11
Migraine with aura	183	95	95	88	88	1	1
Migraine without aura	15	10	10	5	5		
Miller Fisher syndrome	5	5	5				
Mononeuritis	6	6	6				

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System Organ Class

Nervous system disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Mononeuropathy	6	6	6				
Mononeuropathy multiplex	5	5	5				
Monoparesis	122	79	79	43	43	2	2
Monoplegia	139	136	136	3	3		
Morton's neuralgia	1	1	1				
Motor dysfunction	147	75	75	72	72	1	1
Movement disorder	688	201	201	487	487	2	2
Multiple sclerosis	97	95	95	2	2	1	1
Multiple sclerosis relapse	63	62	62	1	1	2	2
Muscle contractions involuntary	144	43	43	101	101		
Muscle spasticity	31	18	18	13	13		
Muscle tone disorder	2	2	2				
Myasthenia gravis	32	30	30	2	2		
Myasthenia gravis crisis	7	7	7				
Myelitis transverse	55	54	54	1	1		
Myelopathy	4	4	4				
Myoclonic epilepsy	2	2	2				
Myoclonus	70	41	41	29	29		
Narcolepsy	15	15	15				
Nerve compression	61	23	23	38	38		
Nerve degeneration	2	2	2				
Nervous system disorder	208	122	122	86	86		
Neuralgia	917	347	347	569	570	1	1
Neuralgic amyotrophy	41	27	27	14	14	1	1
Neuritis	62	28	28	34	34		
Neuritis cranial	5	5	5				
Neuroleptic malignant syndrome	1	1	1				

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System Organ Class

Nervous system disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Neurological decompensation	5	4	4	1	1		
Neurological symptom	96	59	59	37	37	2	2
Neurologic neglect syndrome	6	6	6				
Neuromuscular pain	11	4	4	7	7		
Neuromyelitis optica spectrum disorder	8	8	8				
Neuromyopathy	7	7	7				
Neuromyotonia	1	1	1				
Neuronal neuropathy	1	1	1				
Neuropathy peripheral	396	387	387	9	9	1	1
Neurosarcoidosis	1	1	1				
Neurotoxicity	2	2	2				
New daily persistent headache	4			4	4		
Noninfectious myelitis	1	1	1				
Noninfective encephalitis	10	10	10				
Normal pressure hydrocephalus	3	3	3				
Notalgia paraesthetica	1			1	1		
Numb chin syndrome	2	2	2				
Nystagmus	73	39	39	34	34		
Occipital neuralgia	29	16	16	13	13		
Oculofacial paralysis	3	3	3				
Olfactory nerve disorder	3			3	3		
Ophthalmic migraine	54	19	19	35	35		
Ophthalmoplegic migraine	1			1	1		
Opisthotonus	4	4	4				
Optic neuritis	65	64	64	1	1	1	1
Oromandibular dystonia	1			1	1		
Orthostatic intolerance	8	4	4	4	4		

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Nervous system disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Orthostatic tremor	2			2	2		
Osmotic demyelination syndrome	1	1	1				
Paraesthesia	9525	2652	2654	6863	6871	19	19
Paraesthesia mucosal	11	6	6	4	5		
Paralysis	295	290	290	5	5	1	1
Paralysis recurrent laryngeal nerve	1	1	1				
Paraparesis	23	23	23				
Paraplegia	9	9	9				
Paresis	79	44	44	35	35		
Paresis cranial nerve	5	3	3	2	2		
Parkinsonian gait	1			1	1		
Parkinsonian rest tremor	1			1	1		
Parkinsonism	13	10	10	3	3		
Parkinson's disease	35	35	35				
Parosmia	444	98	98	345	346		
Paroxysmal sympathetic hyperactivity	2	2	2				
Partial seizures	37	37	37				
Partial seizures with secondary generalisation	2	2	2				
Patient elopement	8	2	2	6	6		
Peripheral motor neuropathy	3	3	3				
Peripheral nerve lesion	3	2	2	1	1		
Peripheral nerve palsy	4	1	1	3	3		
Peripheral nerve paresis	2	2	2				
Peripheral paralysis	6	6	6				
Peripheral sensorimotor neuropathy	2	2	2				
Peripheral sensory neuropathy	20	13	13	7	7		
Periventricular leukomalacia	1	1	1				

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System Organ Class

Nervous system disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Peroneal nerve palsy	25	17	17	8	8		
Persistent genital arousal disorder	1			1	1		
Persistent postural-perceptual dizziness	10	6	6	4	4		
Petit mal epilepsy	54	54	54				
Phantom limb syndrome	8	3	3	5	5		
Pineal gland cyst	1	1	1				
Piriformis syndrome	1			1	1		
Pleocytosis	6	5	5	1	1		
Polyneuropathy	41	41	41			1	1
Polyneuropathy chronic	1			1	1		
Polyneuropathy in malignant disease	1	1	1				
Posterior reversible encephalopathy syndrome	5	5	5				
Post herpetic neuralgia	42	22	22	20	20		
Postictal paralysis	1	1	1				
Postictal state	9	5	5	4	4		
Post polio syndrome	1	1	1				
Post stroke epilepsy	1	1	1				
Post stroke seizure	1	1	1				
Post-traumatic neuralgia	1			1	1		
Postural tremor	1	1	1				
Precerebral artery thrombosis	1	1	1				
Presbyastasis	1	1	1				
Presyncope	1992	767	769	1219	1223	4	4
Primary cough headache	4	2	2	2	2		
Primary headache associated with sexual activity	2	2	2				
Progressive supranuclear palsy	1	1	1				
Psychogenic seizure	8	7	7	1	1		

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System Organ Class

Nervous system disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Psychomotor hyperactivity	75	27	27	48	48		
Psychomotor skills impaired	14	5	5	9	9		
Pudendal canal syndrome	2	1	1	1	1		
Putamen haemorrhage	6	6	6				
Pyramidal tract syndrome	1	1	1				
Quadrantanopia	3	3	3				
Quadriparesis	13	13	13				
Quadriplegia	6	6	6				
Radial nerve palsy	7	4	4	3	3		
Radicular pain	3			3	3		
Radiculitis brachial	24	17	17	7	7		
Radiculopathy	24	14	14	10	10		
Reduced facial expression	26	11	11	15	15		
Reflexes abnormal	5	2	2	3	3		
Relapsing-remitting multiple sclerosis	1	1	1				
Repetitive speech	3	1	1	2	2		
Resting tremor	8	3	3	5	5		
Restless arm syndrome	3	1	1	2	2		
Restless legs syndrome	115	43	43	72	72	1	1
Retinal migraine	17	11	11	6	6		
Retrograde amnesia	7	3	3	4	4		
Reversed hot-cold sensation	8	2	2	6	6		
Reversible cerebral vasoconstriction syndrome	3	3	3				
Ruptured cerebral aneurysm	8	8	8				
Sciatica	181	72	72	109	109		
Sciatic nerve neuropathy	5	2	2	3	3		
Sciatic nerve palsy	1			1	1		

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System Organ Class

Nervous system disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Secondary cerebellar degeneration	2	2	2				
Sedation	49	13	13	36	36		
Seizure	1160	1132	1132	28	28	1	1
Seizure anoxic	2	2	2				
Seizure cluster	4	4	4				
Seizure like phenomena	17	17	17				
Senile dementia	3	3	3				
Sensorimotor disorder	8	6	6	2	2		
Sensory disturbance	463	134	135	328	328		
Sensory loss	214	110	110	104	104	1	1
Sensory overload	4	3	3	1	1		
Sensory processing disorder	1	1	1				
Serotonin syndrome	2	2	2				
Simple partial seizures	2	2	2				
Sinus headache	275	115	115	160	160	2	2
Sleep deficit	31	8	8	23	23		
Sleep paralysis	18	5	5	13	13		
Slow response to stimuli	12	5	5	7	7		
Slow speech	34	17	17	17	17		
Small fibre neuropathy	6	3	3	3	3		
Somnolence	4373	910	911	3461	3462	6	6
Spasmodic dysphonia	1			1	1		
Speech disorder	574	310	310	264	264	2	2
Speech disorder developmental	4			4	4		
Spinal claudication	1	1	1				
Spinal cord compression	2	2	2				
Spinal cord disorder	8	8	8				

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System Organ Class

Nervous system disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Spinal cord infarction	4	4	4				
Spinal cord ischaemia	3	3	3				
Spinal cord oedema	1	1	1				
Spinal epidural haematoma	3	3	3				
Spinal epidural haemorrhage	1	1	1				
Spinal meningeal cyst	1	1	1				
Spinal stroke	1	1	1				
Spinal subdural haemorrhage	1	1	1				
Spinal vascular disorder	1	1	1				
Status epilepticus	86	86	86				
Status migrainosus	3	3	3				
Stiff leg syndrome	1	1	1				
Stiff person syndrome	1			1	1		
Stroke in evolution	2	2	2				
Stupor	41	15	15	26	26		
Subacute inflammatory demyelinating polyneuropathy	1	1	1				
Subarachnoid haemorrhage	100	100	100				
Sudden onset of sleep	8	8	8				
Superior sagittal sinus thrombosis	10	10	10				
Sympathicotonia	3	1	1	2	2		
Synaesthesia	1			1	1		
Syncope	3193	3109	3113	80	80	24	24
Synkinesis	1	1	1				
Tardive dyskinesia	5	5	5				
Taste disorder	700	143	143	557	557		
Temporal lobe epilepsy	2	2	2				
Tension headache	421	187	187	234	234	2	2

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System Organ Class

Nervous system disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Thalamic infarction	13	13	13				
Thalamus haemorrhage	9	9	9				
Thermohyperaesthesia	1			1	1		
Thermohypoaesthesia	1			1	1		
Thoracic outlet syndrome	4	2	2	2	2		
Thrombotic cerebral infarction	5	5	5				
Thrombotic stroke	18	18	18				
Thunderclap headache	10	8	8	2	2		
Tongue biting	20	15	15	5	5		
Tongue paralysis	17	16	16	1	1		
Tonic clonic movements	22	22	22				
Tonic convulsion	28	26	26	2	2		
Tonic posturing	1	1	1				
Toxic neuropathy	1	1	1				
Transient aphasia	9	9	9				
Transient global amnesia	33	22	22	11	11	1	1
Transient ischaemic attack	511	509	509	2	2	3	3
Transverse sinus stenosis	2	2	2				
Transverse sinus thrombosis	8	8	8				
Tremor	3480	1344	1349	2127	2131	11	11
Trigeminal nerve disorder	30	14	14	16	16		
Trigeminal nerve paresis	3	3	3				
Trigeminal neuralgia	124	54	54	70	70		
Trigeminal neuritis	7	4	4	3	3		
Trigeminal palsy	5	5	5				
Tumefactive multiple sclerosis	1	1	1				
Tunnel vision	45	43	43	2	2		

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System Organ Class

Nervous system disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Typical aura without headache	6	4	4	2	2		
Ulnar nerve palsy	4	3	3	1	1		
Ulnar neuritis	2	2	2				
Unresponsive to stimuli	179	177	177	2	2		
Vagus nerve disorder	6	6	6				
Vascular dementia	9	9	9				
Vascular encephalopathy	6	6	6				
Vascular headache	12	7	7	5	5		
Vascular parkinsonism	1	1	1				
Vertebral artery aneurysm	1	1	1				
Vertebral artery dissection	5	5	5				
Vertebral artery occlusion	3	3	3				
Vertebral artery stenosis	2	2	2				
Vertebral artery thrombosis	2	2	2				
Vertebrobasilar insufficiency	1	1	1				
Vertebrobasilar stroke	4	4	4				
Vertigo CNS origin	3	1	1	2	2		
Vestibular migraine	13	10	10	3	3		
Vibratory sense increased	3			3	3		
Visual perseveration	1	1	1				
Visuospatial deficit	1	1	1				
VIth nerve disorder	3	2	2	1	1		
VIth nerve paralysis	30	30	30				
VIth nerve paresis	3	1	1	2	2		
Vocal cord paralysis	6	4	4	2	2		
Vocal cord paresis	1			1	1		
White matter lesion	12	8	8	4	4		

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System Organ Class

Nervous system disorders

		Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
Preferred Term	*Total # of Spontaneous AE*	I	C	I	C	I	C
Writer's cramp	1	1	1				
Total:	181529	57219	57276	124114	124253	460	460

System Organ Class

Pregnancy, puerperium and perinatal conditions

		Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
Preferred Term	*Total # of Spontaneous AE*	I	C	I	C	I	C
Abortion	8	8	8			1	1
Abortion early	2	2	2				
Abortion missed	21	21	21				
Abortion spontaneous	272	265	265	7	7	2	2
Abortion threatened	2	2	2				
Anembryonic gestation	5	5	5				
Arrested labour	2	1	1	1	1		
Cephalhaematoma	1	1	1				
Cervical incompetence	1	1	1				
Cervix dystocia	1	1	1				
Complication of pregnancy	2			2	2		
Decidual cast	1	1	1				
Ectopic pregnancy	4	4	4				
Face presentation	1			1	1		
Foetal death	19	19	19				
Foetal growth restriction	12	12	12				
Foetal hypokinesia	6	4	4	2	2		
Gestational diabetes	7	6	6	1	1		
Haemorrhage in pregnancy	2	2	2				
High risk pregnancy	1			1	1		

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System Organ Class

Pregnancy, puerperium and perinatal conditions

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Hydrops foetalis	2	1	1	1	1		
Labour complication	1			1	1		
Labour pain	1			1	1		
Morning sickness	17	12	12	5	5	1	1
Neonatal disorder	1	1	1				
Oligohydramnios	1	1	1				
Placental disorder	1	1	1				
Postpartum haemorrhage	2	1	1	1	1		
Pre-eclampsia	2	2	2				
Pregnancy	13	1	1	12	12		
Pregnancy after post coital contraception	3	2	2	1	1		
Pregnancy on contraceptive	1	1	1				
Pregnancy on oral contraceptive	1	1	1				
Pregnancy with contraceptive device	3	3	3				
Pregnancy with implant contraceptive	2	2	2				
Premature baby	15	13	13	2	2		
Premature delivery	2	2	2				
Premature labour	6	5	5	1	1		
Premature rupture of membranes	3	3	3				
Premature separation of placenta	1	1	1				
Preterm premature rupture of membranes	2	2	2				
Retroplacental haematoma	1	1	1				
Risk of future pregnancy miscarriage	1			1	1		
Small for dates baby	1	1	1				
Stillbirth	7	7	7				
Threatened labour	1			1	1		
Twin pregnancy	2			2	2		

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System Organ Class

Pregnancy, puerperium and perinatal conditions

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Umbilical cord abnormality	1	1	1				
Umbilical cord thrombosis	1	1	1				
Unintended pregnancy	1			1	1		
Uterine contractions abnormal	5	4	4	1	1		
Uterine contractions during pregnancy	5	2	2	3	3		
Total:	476	427	427	49	49	4	4

System Organ Class

Product issues

Preferred Term	*Total # of Spontaneous AE*	Spontaneous			
		Serious		Nonserious	
		I	C	I	C
Device breakage	1	1	1		
Device connection issue	1			1	1
Device infusion issue	1	1	1		
Device issue	5			5	5
Device leakage	1			1	1
Device loosening	1	1	1		
Device occlusion	1			1	1
Device pacing issue	1	1	1		
Device power source issue	1			1	1
Device stimulation issue	1			1	1
Device temperature issue	1			1	1
Embedded device	1	1	1		
Lead dislodgement	1	1	1		
Liquid product physical issue	53			53	53
Manufacturing product shipping issue	1			1	1
Needle issue	53	2	2	49	51

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System Organ Class

Product issues

Preferred Term	*Total # of Spontaneous AE*	Spontaneous			
		Serious		Nonserious	
		I	C	I	C
Oversensing	16	8	8	8	8
Patient-device incompatibility	1			1	1
Physical product label issue	1			1	1
Product availability issue	2	1	1	1	1
Product closure issue	1			1	1
Product colour issue	46			46	46
Product complaint	48	2	2	45	46
Product compounding quality issue	1			1	1
Product container issue	8			8	8
Product contamination	4			4	4
Product contamination physical	8			8	8
Product delivery mechanism issue	3			3	3
Product deposit	6			6	6
Product expiration date issue	4			4	4
Product formulation issue	1	1	1		
Product leakage	41			39	41
Product lot number issue	3			3	3
Product odour abnormal	4			4	4
Product origin unknown	1			1	1
Product packaging difficult to open	1			1	1
Product packaging issue	1			1	1
Product packaging quantity issue	25			25	25
Product physical issue	11			11	11
Product quality issue	75			75	75
Product reconstitution quality issue	2			2	2
Product sterility lacking	1			1	1
Product substitution issue	1			1	1

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System Organ Class

Product issues

Preferred Term	*Total # of Spontaneous AE*	Spontaneous			
		Serious		Nonserious	
		I	C	I	C
Product supply issue	76			76	76
Product taste abnormal	7			7	7
Product temperature excursion issue	4123	4	4	4029	4119
Suspected counterfeit product	17			17	17
Suspected product quality issue	5			5	5
Syringe issue	41			40	41
Thrombosis in device	5	5	5		
Undersensing	2	1	1	1	1
Total:	4716	30	30	4590	4686

System Organ Class

Psychiatric disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Abnormal behaviour	51	21	21	30	30		
Abnormal dreams	206	46	46	160	160		
Abnormal sleep-related event	5	1	1	4	4		
Abulia	3			3	3		
Acute psychosis	5	5	5				
Acute stress disorder	8	7	7	1	1		
Adjustment disorder	1			1	1		
Adjustment disorder with depressed mood	3	3	3				
Adjustment disorder with mixed anxiety and depressed mooc	1	1	1				
Affective ambivalence	1			1	1		
Affective disorder	13	3	3	10	10		
Affect lability	26	9	9	17	17		
Aggression	60	38	38	22	22	1	1

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System Organ Class

Psychiatric disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Agitated depression	2	2	2				
Agitation	350	126	126	224	224	2	2
Alcoholic hangover	1	1	1				
Alcoholism	2	1	1	1	1		
Alcohol problem	1			1	1		
Alexithymia	1			1	1		
Anger	52	14	14	38	38		
Anhedonia	2	1	1	1	1		
Anorgasmia	2	1	1	1	1		
Antisocial personality disorder	1	1	1				
Anxiety	1684	499	500	1180	1184	2	2
Anxiety disorder	11	4	4	7	7		
Anxiety disorder due to a general medical condition	1			1	1		
Apathy	120	54	54	66	66		
Attention deficit hyperactivity disorder	8	2	2	6	6		
Autism spectrum disorder	3	3	3				
Automatism	1	1	1				
Autoscopy	18	9	9	9	9		
Aversion	3			3	3		
Behaviour disorder	28	20	20	8	8		
Belligerence	1	1	1				
Binge eating	1	1	1				
Bipolar disorder	7	7	7				
Bipolar I disorder	1	1	1				
Blunted affect	1			1	1		
Body dysmorphic disorder	1	1	1				
Borderline personality disorder	1			1	1		

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System Organ Class

Psychiatric disorders

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		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Boredom	1			1	1		
Bradyphrenia	80	39	39	41	41	1	1
Bruxism	19	10	10	9	9		
Bulimia nervosa	1	1	1				
Burnout syndrome	4	2	2	2	2		
Catatonia	6	4	4	2	2		
Change in sustained attention	1			1	1		
Chronic idiopathic pain syndrome	1			1	1		
Clang associations	1			1	1		
Claustrophobia	3			3	3		
Clinomania	1			1	1		
Communication disorder	31	19	19	12	12		
Completed suicide	6	6	6				
Compulsions	1	1	1				
Confusional arousal	1	1	1				
Confusional state	1725	895	896	829	829	13	13
Constricted affect	1	1	1				
Conversion disorder	12	7	7	5	5		
Coprolalia	1			1	1		
Cyclothymic disorder	1	1	1				
Daydreaming	17	5	5	12	12		
Decreased interest	20	9	9	11	11		
Deja vu	2	2	2				
Delirium	239	237	237	2	2		
Delirium febrile	5	5	5				
Delusion	35	19	19	16	16		
Delusional disorder, unspecified type	2	2	2				

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Psychiatric disorders

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		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Delusional perception	8	3	3	5	5		
Depersonalisation/derealisation disorder	9	3	3	6	6		
Depressed mood	410	159	159	250	251	1	1
Depression	306	151	151	155	155		
Depression suicidal	5	5	5				
Depressive symptom	4	2	2	2	2		
Derealisation	30	12	12	18	18		
Discouragement	8			8	8		
Disinhibition	2	1	1	1	1		
Disorganised speech	18	12	12	6	6		
Disorientation	592	315	315	277	277	4	4
Dissociation	46	19	19	27	27		
Dissociative amnesia	1			1	1		
Dissociative disorder	6	1	1	5	5		
Distractibility	11	2	2	9	9		
Disturbance in sexual arousal	1	1	1				
Disturbance in social behaviour	5			5	5		
Drug abuse	1	1	1				
Drug dependence	1			1	1		
Dysphemia	41	22	22	19	19		
Dysphoria	98	59	59	39	39		
Dyssomnia	2			2	2		
Eating disorder	210	63	63	147	147	1	1
Echolalia	1			1	1		
Emotional disorder	100	35	35	65	65		
Emotional distress	67	36	36	31	31		
Emotional poverty	2	2	2				

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System Organ Class

Psychiatric disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Enuresis	21	13	13	8	8		
Euphoric mood	75	19	19	56	56		
Executive dysfunction	1	1	1				
Exhibitionism	1			1	1		
Exploding head syndrome	4	3	3	1	1		
Factitious disorder	2	2	2				
Fear	128	32	32	96	96		
Fear of death	25	5	5	20	20		
Fear of disease	3	1	1	2	2		
Fear of falling	10	3	3	7	7		
Fear of injection	12	1	1	11	11		
Fear-related avoidance of activities	1			1	1		
Feeling guilty	1	1	1				
Feeling of despair	33	11	11	22	22		
Feelings of worthlessness	1			1	1		
Flashback	2	2	2				
Flat affect	15	3	3	12	12		
Frustration tolerance decreased	40	4	4	36	36		
Gastrointestinal somatic symptom disorder	1			1	1		
Generalised anxiety disorder	5	2	2	3	3		
Grief reaction	1	1	1				
Habit cough	10	3	3	7	7		
Hallucination	310	306	307	3	3	3	3
Hallucination, auditory	38	38	38			1	1
Hallucination, olfactory	11	11	11				
Hallucinations, mixed	10	10	10				
Hallucination, tactile	2	2	2				

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System Organ Class

Psychiatric disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Hallucination, visual	92	91	91	1	1		
Head banging	8	3	3	5	5		
Helplessness	6	2	2	4	4		
Homicidal ideation	1			1	1		
Hostility	3	2	2	1	1		
Hydrophobia	1			1	1		
Hyperarousal	1			1	1		
Hypersexuality	2	1	1	1	1		
Hypersomnia-bulimia syndrome	2	2	2				
Hypervigilance	8	3	3	5	5		
Hypnagogic hallucination	3	3	3				
Hypnopompic hallucination	2	2	2				
Hypomania	1	1	1				
Hyposomnia	1	1	1				
Illness anxiety disorder	2			2	2		
Illusion	19	7	7	12	12		
Immunisation anxiety related reaction	15	5	5	10	10		
Impaired reasoning	2	1	1	1	1		
Impatience	2			2	2		
Imperception	3	2	2	1	1		
Impulsive behaviour	1			1	1		
Inappropriate affect	14	9	9	5	5		
Indifference	6	5	5	1	1		
Initial insomnia	196	14	14	182	182		
Insomnia	4225	1025	1025	3199	3200	3	3
Intentional self-injury	7	7	7				
Intermittent explosive disorder	1			1	1		

* I=Interval, C=Cumulative
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System Organ Class

Psychiatric disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Intrusive thoughts	5	2	2	3	3		
Irritability	1034	127	127	907	907		
Lack of spontaneous speech	18	12	12	6	6		
Laziness	18	2	2	16	16		
Learning disability	3	1	1	2	2		
Learning disorder	1	1	1				
Libido decreased	11	3	3	8	8		
Libido disorder	2			2	2		
Libido increased	5			5	5		
Listless	72	18	18	54	54		
Logorrhoea	10	6	6	4	4		
Loss of libido	14	5	5	9	9		
Major depression	11	11	11				
Mania	13	8	8	5	5		
Mental disorder	75	23	23	52	52		
Mental fatigue	150	100	100	50	50		
Mental status changes	18	6	6	12	12		
Middle insomnia	197	52	52	145	145		
Mixed anxiety and depressive disorder	3	1	1	2	2		
Mood altered	68	23	23	45	45		
Mood disorder due to a general medical condition	1	1	1				
Mood swings	55	29	29	26	26		
Morbid thoughts	1			1	1		
Morose	4	1	1	3	3		
Mutism	27	15	15	12	12		
Near death experience	61	57	57	4	4		
Negative thoughts	4	4	4				

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System Organ Class

Psychiatric disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Neglect of personal appearance	1			1	1		
Nervousness	553	144	144	407	409		
Neuropsychiatric symptoms	2	1	1	1	1		
Neurosis	1			1	1		
Nightmare	240	77	77	163	163		
Nosophobia	1	1	1				
Obsessive-compulsive personality disorder	1			1	1		
Obsessive-compulsive symptom	2	1	1	1	1		
Obsessive thoughts	1	1	1				
Oppositional defiant disorder	1	1	1				
Organic brain syndrome	4	3	3	1	1		
Osmophobia	1	1	1				
Panic attack	237	89	90	146	147		
Panic disorder	23	8	8	15	15		
Panic reaction	92	33	33	59	59		
Paramnesia	3	3	3				
Paranoia	38	18	18	20	20		
Paranoid personality disorder	1			1	1		
Parasomnia	1			1	1		
Perinatal depression	3	2	2	1	1		
Persecutory delusion	4	2	2	2	2		
Persistent depressive disorder	5	3	3	2	2		
Personality change	27	19	19	8	8		
Personality disorder	5	2	2	3	3		
Phobia	2	1	1	1	1		
Phonophobia	11	5	5	6	6		
Poor quality sleep	380	111	111	268	269	3	3

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System Organ Class

Psychiatric disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Post-traumatic stress disorder	10	7	7	3	3		
Posturing	2	1	1	1	1		
Poverty of thought content	1			1	1		
Pressure of speech	3	2	2	1	1		
Pseudodementia	1	1	1				
Psychiatric decompensation	2	1	1	1	1		
Psychiatric symptom	16	7	7	9	9		
Psychogenic erectile dysfunction	1			1	1		
Psychogenic pseudosyncope	1			1	1		
Psychological factor affecting medical condition	1	1	1				
Psychological trauma	2	1	1	1	1		
Psychomotor retardation	6	3	3	3	3		
Psychotic behaviour	1	1	1				
Psychotic disorder	33	21	21	12	12		
Psychotic disorder due to a general medical condition	1	1	1				
Psychotic symptom	4	4	4				
Purging	1	1	1				
Reading disorder	11	4	4	7	7		
Restlessness	492	143	143	349	349	1	1
Schizophrenia	4	4	4				
Seasonal affective disorder	1			1	1		
Selective eating disorder	2	1	1	1	1		
Self esteem decreased	1			1	1		
Self-injurious ideation	4	3	3	1	1		
Sense of a foreshortened future	4	2	2	2	2		
Sitophobia	1			1	1		
Sleep attacks	8	2	2	6	6		

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System Organ Class

Psychiatric disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Sleep disorder	943	239	239	704	704		
Sleep disorder due to a general medical condition	34	9	9	25	25		
Sleep disorder due to general medical condition, hypersomni	1			1	1		
Sleep disorder due to general medical condition, insomnia ty	47	21	21	26	26		
Sleep inertia	1	1	1				
Sleep talking	8	1	1	7	7		
Sleep terror	16	8	8	8	8		
Social avoidant behaviour	6	3	3	3	3		
Social fear	1	1	1				
Social (pragmatic) communication disorder	1	1	1				
Soliloquy	6			6	6		
Somatic symptom disorder	17	9	9	8	8		
Somnambulism	12	1	1	11	11		
Sopor	25	17	17	8	8	3	3
Speech sound disorder	5	3	3	2	2		
Staring	15	11	12	3	3		
Stereotypy	3	3	3				
Stress	181	48	48	132	133		
Substance abuse	1	1	1				
Substance-induced psychotic disorder	1	1	1				
Suicidal behaviour	3	3	3				
Suicidal ideation	71	68	68	3	3		
Suicide attempt	14	14	14				
Suspiciousness	2	1	1	1	1		
Tachyphrenia	11	4	4	7	7		
Tearfulness	45	23	23	22	22		
Tension	84	19	19	65	65		

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System Organ Class

Psychiatric disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Terminal insomnia	23	5	5	18	18		
Thanatophobia	1			1	1		
Thinking abnormal	121	32	32	89	89		
Thought blocking	1	1	1				
Tic	32	14	14	18	18		
Time perception altered	1			1	1		
Trance	3			3	3		
Verbigeration	1			1	1		
Violence-related symptom	1			1	1		
Vomiting psychogenic	2	1	1	1	1		
Total:	18151	6522	6527	11613	11624	39	39

System Organ Class

Renal and urinary disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Acute kidney injury	223	221	221	2	2	1	1
Albuminuria	2	2	2				
Anti-glomerular basement membrane disease	1	1	1				
Anuria	32	31	31	1	1	1	1
Azotaemia	8	8	8				
Bilirubinuria	1	1	1				
Bladder dilatation	3	2	2	1	1		
Bladder discomfort	13	2	2	11	11		
Bladder disorder	24	11	11	13	13		
Bladder dysfunction	8	6	6	2	2		
Bladder fibrosis	1	1	1				

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* AE=Adverse Event
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System Organ Class

Renal and urinary disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Bladder hypertrophy	1	1	1				
Bladder irritation	4	1	1	3	3		
Bladder obstruction	3	3	3				
Bladder pain	28	15	15	13	13		
Bladder spasm	8	3	3	5	5		
Bladder sphincter atony	2	2	2				
Calculus bladder	1			1	1		
Calculus urinary	3			3	3		
Choluria	5	2	2	3	3		
Chromaturia	130	35	35	95	95		
Chronic kidney disease	33	32	32	1	1		
Costovertebral angle tenderness	6	1	1	5	5		
Cystitis haemorrhagic	7	7	7				
Cystitis interstitial	3	2	2	1	1		
Cystitis-like symptom	1	1	1				
Cystitis noninfective	7	2	2	5	5		
Diabetic nephropathy	1			1	1		
Dysuria	196	80	80	116	116		
End stage renal disease	2	2	2				
Genitourinary symptom	2	2	2				
Glomerulonephritis	5	5	5				
Glomerulonephritis acute	1	1	1				
Glomerulonephritis chronic	1	1	1				
Glomerulonephritis minimal lesion	17	17	17				
Glomerulonephritis rapidly progressive	1	1	1				
Haematuria	136	77	77	59	59		
Haemoglobinuria	2	2	2				

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System Organ Class

Renal and urinary disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Haemorrhage urinary tract	30	30	30				
Hydronephrosis	3	3	3			1	1
Hypertonic bladder	4	1	1	3	3		
Hypotonic urinary bladder	1	1	1				
IgA nephropathy	5	5	5				
Incontinence	69	41	41	28	28		
Ketonuria	1	1	1				
Kidney fibrosis	1	1	1				
Kidney small	1	1	1				
Leukocyturia	11	5	5	6	6		
Loss of bladder sensation	2	2	2				
Lower urinary tract symptoms	2	2	2				
Lupus nephritis	1	1	1				
Microalbuminuria	1	1	1				
Micturition disorder	14	4	4	10	10		
Micturition frequency decreased	2			2	2		
Micturition urgency	63	32	32	31	31		
Mixed incontinence	1			1	1		
Myoglobinuria	1	1	1				
Nephritis	6	6	6				
Nephritis allergic	1	1	1				
Nephrogenic diabetes insipidus	1	1	1				
Nephrolithiasis	56	56	56			1	1
Nephropathy	11	8	8	3	3		
Nephrosclerosis	2	2	2				
Nephrotic syndrome	36	36	36				
Neurogenic bladder	3	3	3				

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System Organ Class

Renal and urinary disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Nocturia	16	2	2	14	14		
Oliguria	19	10	10	9	9		
Paroxysmal nocturnal haemoglobinuria	2	2	2				
Perinephric collection						1	1
Pollakiuria	218	58	58	159	160	1	1
Polyuria	60	18	18	42	42		
Prerenal failure	7	7	7				
Proteinuria	25	14	14	11	11		
Renal artery dissection	1	1	1				
Renal artery stenosis	1	1	1				
Renal artery thrombosis	3	3	3				
Renal atrophy	2	2	2				
Renal colic	21	12	12	9	9		
Renal cyst	16	7	7	9	9		
Renal cyst haemorrhage	1	1	1				
Renal disorder	64	35	35	29	29		
Renal failure	164	164	164				
Renal haemorrhage	4	4	4				
Renal hypertrophy	1	1	1				
Renal impairment	87	87	87				
Renal infarct	9	9	9				
Renal injury	4	4	4				
Renal ischaemia	1	1	1				
Renal mass	2	2	2				
Renal pain	348	142	142	206	206		
Renal tubular disorder	1	1	1				
Renal tubular injury	1	1	1				

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System Organ Class

Renal and urinary disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Renal tubular necrosis	4	4	4				
Renal vasculitis	2	2	2				
Renal vein thrombosis	1	1	1				
Strangury	3			3	3	1	1
Stress urinary incontinence	3			3	3		
Tubulointerstitial nephritis	5	5	5				
Ureteric dilatation						1	1
Ureteric stenosis	2	2	2				
Ureterolithiasis	1	1	1				
Urethral disorder	1			1	1		
Urethral haemorrhage	1	1	1				
Urethral pain	2			2	2		
Urethral stenosis	1	1	1				
Urethritis noninfective	2			2	2		
Urge incontinence	3	2	2	1	1		
Urinary bladder haemorrhage	4	4	4				
Urinary hesitation	4	1	1	3	3		
Urinary incontinence	188	99	99	89	89		
Urinary retention	98	98	98				
Urinary straining	2	1	1	1	1		
Urinary tract discomfort	2			2	2		
Urinary tract disorder	7	2	2	5	5		
Urinary tract inflammation	8	5	5	3	3		
Urinary tract obstruction	1	1	1				
Urinary tract pain	5	2	2	3	3		
Urine abnormality	21	6	6	15	15		
Urine flow decreased	9	6	6	3	3		

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System Organ Class

Renal and urinary disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Urine odour abnormal	32	9	9	23	23		
Urogenital haemorrhage	2	2	2				
Total:	2743	1670	1670	1072	1073	8	8

System Organ Class

Reproductive system and breast disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Abnormal uterine bleeding	8	6	6	2	2		
Abnormal withdrawal bleeding	1			1	1		
Adenomyosis	3	1	1	2	2		
Adnexal torsion	1	1	1				
Adnexa uteri pain	35	13	13	22	22		
Amenorrhoea	147	58	58	89	89		
Anisomastia	2			2	2		
Aspermia	2			2	2		
Atrophic vulvovaginitis	1	1	1				
Bartholin's cyst	1	1	1				
Benign prostatic hyperplasia	7	3	3	4	4		
Breast atrophy	1			1	1		
Breast calcifications	1			1	1		
Breast cyst	10	3	3	7	7		
Breast discharge	6			6	6		
Breast discolouration	3	1	1	2	2		
Breast discomfort	50	11	11	39	39		
Breast disorder	11	4	4	7	7		
Breast disorder female	1			1	1		

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* AE=Adverse Event
* Multiple adverse events coding to the same Preferred Term may have been reported in some cases. Counts are provided for the number of unique Preferred Terms reported.

System Organ Class

Reproductive system and breast disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Breast engorgement	6	2	2	4	4		
Breast enlargement	17	5	5	12	12		
Breast haematoma	7	5	5	2	2		
Breast haemorrhage	1	1	1				
Breast induration	7	1	1	6	6		
Breast inflammation	26	9	9	17	17		
Breast mass	87	37	37	50	50	1	1
Breast milk discolouration	3			3	3		
Breast oedema	17	6	6	11	11		
Breast pain	710	236	236	474	474	1	1
Breast swelling	195	65	65	130	130		
Breast tenderness	85	24	24	61	61	1	1
Cervical cyst	1			1	1		
Cervical discharge	1	1	1				
Cervical dysplasia	2	1	1	1	1		
Cervical polyp	3	3	3				
Cervix disorder	1	1	1				
Cervix erythema	1	1	1				
Cervix haematoma uterine	1	1	1				
Cervix haemorrhage uterine	1	1	1				
Cervix oedema	1			1	1		
Coital bleeding	1			1	1		
Cystocele	1			1	1		
Dysmenorrhoea	421	262	262	159	159	2	2
Dyspareunia	2	1	1	1	1		
Ejaculation disorder	2			2	2		
Ejaculation failure	2	1	1	1	1		

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System Organ Class

Reproductive system and breast disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Endometrial thickening	3	1	1	2	2		
Endometriosis	29	23	23	6	6		
Epididymal tenderness	1	1	1				
Erectile dysfunction	68	65	65	3	3		
Erection increased	4	3	3	1	1		
Female genital tract fistula	1	1	1				
Female reproductive tract disorder	2	1	1	1	1		
Female sexual dysfunction	1			1	1		
Galactorrhoea	6	5	5	1	1		
Galactostasis	4	1	1	3	3		
Genital blister	4	2	2	2	2		
Genital burning sensation	3			3	3		
Genital discomfort	3	1	1	2	2		
Genital disorder	2			2	2		
Genital erythema	2			2	2		
Genital haemorrhage	32	29	29	3	3		
Genital lesion	6			6	6		
Genital pain	9	5	5	4	4		
Genital paraesthesia	3			3	3		
Genital rash	3	1	1	2	2		
Genital swelling	2	1	1	1	1		
Genital tract inflammation	3			3	3		
Genital ulceration	5	3	3	2	2		
Gynaecomastia	8	2	2	6	6		
Haematospermia	6	3	3	3	3		
Heavy menstrual bleeding	880	483	483	397	397	1	1
Hypomenorrhoea	64	25	25	39	39	1	1

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System Organ Class

Reproductive system and breast disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Infertility	5	2	2	3	3		
Infertility female	2	1	1	1	1		
Intermenstrual bleeding	293	96	96	196	197		
Labia enlarged	1	1	1				
Lactation disorder	8	4	4	4	4		
Lactation puerperal increased	1			1	1		
Menometrorrhagia	8	6	6	2	2		
Menopausal disorder	1	1	1				
Menopausal symptoms	12	4	4	8	8		
Menstrual discomfort	7	4	4	3	3		
Menstrual disorder	451	130	130	321	321	2	2
Menstruation delayed	349	140	140	209	209	1	1
Menstruation irregular	515	188	188	327	327	2	2
Nipple disorder	3			3	3		
Nipple exudate bloody	2	1	1	1	1		
Nipple pain	42	12	12	30	30		
Nipple swelling	16	3	3	13	13		
Oedema genital	5	3	3	2	2		
Oligomenorrhoea	43	18	18	25	25		
Orchitis noninfective	2			2	2		
Organic erectile dysfunction	1			1	1		
Ovarian cyst	10	3	3	7	7		
Ovarian cyst ruptured	5	4	4	1	1		
Ovarian disorder	1	1	1				
Ovarian enlargement	1			1	1		
Ovarian haemorrhage	2	2	2				
Ovarian vein thrombosis	2	2	2				

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System Organ Class

Reproductive system and breast disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Ovulation disorder	4	1	1	3	3		
Ovulation pain	11	8	8	3	3		
Painful ejaculation	1	1	1				
Pelvic discomfort	4	3	3	1	1		
Pelvic floor muscle weakness	1	1	1				
Pelvic haematoma	1			1	1		
Pelvic haemorrhage	6	6	6				
Pelvic pain	124	50	50	74	74		
Penile burning sensation	1			1	1		
Penile discomfort	1			1	1		
Penile erythema	2			2	2		
Penile exfoliation	1			1	1		
Penile haemorrhage	4	4	4				
Penile oedema	2	1	1	1	1		
Penile pain	1			1	1		
Penile rash	1			1	1		
Penile swelling	5	2	2	3	3		
Penile vein thrombosis	1	1	1				
Penis disorder	6	2	2	4	4		
Perineal pain	6	3	3	3	3		
Plasma cell mastitis	1			1	1		
Polycystic ovaries	7	4	4	3	3		
Polymenorrhoea	145	51	51	94	94	1	1
Postmenopausal haemorrhage	127	119	119	8	8	1	1
Premature menopause	3	2	2	1	1		
Premature ovulation	1			1	1		
Premenstrual dysphoric disorder	2	2	2				

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System Organ Class

Reproductive system and breast disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Premenstrual headache	2	1	1	1	1		
Premenstrual pain	19	8	8	11	11		
Premenstrual syndrome	30	8	8	22	22		
Priapism	3	2	2	1	1		
Prostatic disorder	4			4	4		
Prostatic pain	1	1	1				
Prostatitis	13	8	8	5	5		
Prostatomegaly	9	2	2	7	7		
Pruritus genital	4	1	1	3	3		
Reproductive tract disorder	1			1	1		
Scrotal dermatitis	1			1	1		
Scrotal disorder	1			1	1		
Scrotal erythema	4	2	2	2	2		
Scrotal exfoliation	2	1	1	1	1		
Scrotal inflammation	1			1	1		
Scrotal pain	8	3	3	5	5		
Scrotal swelling	5	3	3	2	2		
Semen discolouration	1	1	1				
Sexual dysfunction	2	1	1	1	1		
Spontaneous penile erection	4			4	4		
Suppressed lactation	19	8	8	11	11		
Testicular disorder	3			3	3		
Testicular pain	49	16	16	33	33		
Testicular retraction	1	1	1				
Testicular swelling	15	4	4	11	11		
Testicular torsion	1	1	1				
Testis discomfort	5	2	2	3	3		

* I=Interval, C=Cumulative
* AE=Adverse Event
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System Organ Class

Reproductive system and breast disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Thrombosis corpora cavernosa	1	1	1				
Uterine cyst	1			1	1		
Uterine disorder	1			1	1		
Uterine enlargement	1			1	1		
Uterine haemorrhage	25	23	23	2	2		
Uterine inflammation	3	2	2	1	1		
Uterine pain	13	7	7	6	6		
Uterine polyp	2	2	2				
Uterine prolapse	1	1	1				
Uterine spasm	11	4	4	7	7		
Vaginal cyst	2	2	2				
Vaginal discharge	24	8	8	16	16		
Vaginal disorder	3	2	2	1	1		
Vaginal haemorrhage	414	221	221	193	193		
Vaginal lesion	2	1	1	1	1		
Vaginal odour	1	1	1				
Vaginal ulceration	2	1	1	1	1		
Varicocele	1			1	1		
Vulval disorder	2	1	1	1	1		
Vulval haemorrhage	9	9	9				
Vulval oedema	3	1	1	2	2		
Vulval ulceration	6	1	1	5	5		
Vulvovaginal burning sensation	12	4	4	8	8		
Vulvovaginal discomfort	5	2	2	3	3		
Vulvovaginal dryness	6	3	3	3	3		
Vulvovaginal erythema	1			1	1		
Vulvovaginal inflammation	1	1	1				

* I=Interval, C=Cumulative
* AE=Adverse Event
* Multiple adverse events coding to the same Preferred Term may have been reported in some cases. Counts are provided for the number of unique Preferred Terms reported.

System Organ Class

Reproductive system and breast disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Vulvovaginal pain	26	11	11	15	15		
Vulvovaginal pruritus	8	1	1	7	7		
Vulvovaginal rash	3	1	1	2	2		
Vulvovaginal swelling	9	4	4	5	5		
Vulvovaginal ulceration	3	3	3				
Withdrawal bleed	2	1	1	1	1		
Total:	6116	2703	2703	3412	3413	14	14

System Organ Class

Respiratory, thoracic and mediastinal disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Acute chest syndrome	1	1	1				
Acute pulmonary oedema	56	56	56				
Acute respiratory distress syndrome	60	60	60				
Acute respiratory failure	93	92	92	1	1	1	1
Adenoidal disorder	1			1	1		
Agonal respiration	1	1	1				
Allergic bronchitis	1			1	1		
Allergic cough	12	6	6	6	6		
Allergic pharyngitis	1	1	1				
Allergic respiratory disease	2			2	2		
Allergic respiratory symptom	6	5	5	1	1		
Allergic sinusitis	7	1	1	6	6		
Alveolitis	2	2	2				
Aphonia	248	96	96	152	152	1	1
Apnoea	49	47	47	2	2		

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* AE=Adverse Event
* Multiple adverse events coding to the same Preferred Term may have been reported in some cases. Counts are provided for the number of unique Preferred Terms reported.

System Organ Class

Respiratory, thoracic and mediastinal disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Apnoeic attack	5	5	5				
Asphyxia	48	46	46	2	2		
Aspiration	51	50	50	1	1		
Asthma	840	462	462	377	378		
Asthma exercise induced	3	2	2	1	1		
Asthma late onset	2	1	1	1	1		
Asthmatic crisis	53	52	52	1	1	4	4
Atelectasis	28	20	20	8	8		
Bradypnoea	3	3	3				
Bronchial disorder	10	5	5	5	5		
Bronchial haemorrhage	1	1	1				
Bronchial hyperreactivity	10	5	5	5	5		
Bronchial irritation	3			3	3		
Bronchial obstruction	6	6	6				
Bronchial oedema	2	2	2				
Bronchial secretion retention	6	1	1	5	5		
Bronchial wall thickening	2	1	1	1	1		
Bronchiectasis	14	14	14				
Bronchitis chronic	5			5	5		
Bronchopneumopathy	4	3	3	1	1		
Bronchospasm	408	218	218	190	190	1	1
Bronchostenosis	7	7	7				
Catarrh	43	10	10	33	33		
Cheyne-Stokes respiration	1	1	1				
Choking	77	76	76	1	1	1	1
Choking sensation	83	48	48	35	35		
Chronic obstructive pulmonary disease	126	95	95	31	31	1	1

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* AE=Adverse Event
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System Organ Class

Respiratory, thoracic and mediastinal disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Chronic respiratory disease	1			1	1		
Chronic respiratory failure	5	5	5				
Cough	7679	2119	2122	5554	5557	12	12
Cough decreased	4			4	4		
Cough variant asthma	10	5	5	5	5		
Cyanosis central	1	1	1				
Cystic lung disease	1			1	1		
Diaphragmalgia	29	10	10	19	19		
Diaphragmatic disorder	4	2	2	2	2		
Diaphragmatic paralysis	1	1	1			1	1
Diaphragmatic spasm	4	2	2	2	2		
Diffuse alveolar damage	2	2	2				
Dry lung syndrome	1	1	1				
Dry throat	329	89	90	239	239	2	2
Dysaesthesia pharynx	3			3	3		
Dysphonia	879	334	336	541	543	3	3
Dyspnoea	11018	5399	5411	5605	5607	32	32
Dyspnoea at rest	58	56	56	2	2	1	1
Dyspnoea exertional	409	218	218	191	191	4	4
Dyspnoea paroxysmal nocturnal	2	1	1	1	1		
Emphysema	26	11	11	15	15		
Eosinophilic bronchitis	1	1	1				
Eosinophilic pneumonia acute	1	1	1				
Epiglottic oedema	6	6	6				
Epistaxis	1261	406	406	855	855	2	2
Glottal incompetence	1	1	1				
Grunting	16	5	5	11	11		

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System Organ Class

Respiratory, thoracic and mediastinal disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Haemoptysis	145	82	82	63	63		
Haemothorax	3	3	3				
Hiccups	38	14	14	24	24		
Hydrothorax	4	4	4				
Hyperactive pharyngeal reflex	2	1	1	1	1		
Hypercapnia	12	11	11	1	1		
Hyperoxia	3	1	1	2	2		
Hypersensitivity pneumonitis	3	3	3				
Hyperventilation	312	175	176	136	136	1	1
Hypocapnia	2	1	1	1	1		
Hypopnoea	118	79	79	39	39		
Hypoventilation	15	15	15				
Hypoxia	209	205	205	4	4	1	1
Idiopathic interstitial pneumonia	1	1	1				
Idiopathic pulmonary fibrosis	7	7	7				
Increased bronchial secretion	16	10	10	6	6		
Increased upper airway secretion	48	18	18	30	30		
Increased viscosity of bronchial secretion	5	4	4	1	1		
Increased viscosity of upper respiratory secretion	25	12	12	13	13		
Interstitial lung disease	51	51	51			1	1
Intranasal hypoaesthesia	4	1	1	3	3		
Intranasal paraesthesia	13	1	1	12	12		
Irregular breathing	23	14	14	9	9		
Laryngeal discomfort	53	27	27	26	26		
Laryngeal disorder	6	3	3	3	3		
Laryngeal dyspnoea	6	6	6				
Laryngeal erythema	1	1	1				

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System Organ Class

Respiratory, thoracic and mediastinal disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Laryngeal inflammation	3	1	1	2	2		
Laryngeal obstruction	11	11	11				
Laryngeal oedema	229	228	228	1	1	1	1
Laryngeal pain	26	7	7	19	19		
Laryngeal stenosis	4	4	4				
Laryngitis allergic	2	2	2				
Laryngospasm	69	50	50	19	19	1	1
Larynx irritation	20	8	8	12	12		
Lower respiratory tract congestion	17	10	10	7	7		
Lung consolidation	5	4	4	1	1		
Lung disorder	168	86	86	82	82	1	1
Lung hyperinflation	2			2	2		
Lung infiltration	35	25	25	10	10		
Lung opacity	21	16	16	5	5		
Meconium aspiration syndrome	1	1	1				
Mediastinal disorder	1			1	1		
Mediastinal haemorrhage	1	1	1				
Mediastinal mass	1			1	1		
Middle lobe syndrome	1	1	1				
Mouth breathing	5	4	4	1	1		
Nasal congestion	1349	236	236	1110	1113	1	1
Nasal crusting	2			2	2		
Nasal discharge discolouration	5			5	5		
Nasal discomfort	142	35	36	106	106		
Nasal disorder	18	3	3	15	15		
Nasal dryness	51	13	13	37	38		
Nasal inflammation	4	1	1	3	3		

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System Organ Class

Respiratory, thoracic and mediastinal disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Nasal mucosa atrophy	1			1	1		
Nasal mucosal disorder	4	1	1	3	3		
Nasal obstruction	49	16	16	33	33		
Nasal odour	5	3	3	2	2		
Nasal oedema	64	23	23	41	41		
Nasal pruritus	50	12	12	38	38		
Nasal turbinate hypertrophy	1			1	1		
Nasal ulcer	2			2	2		
Neonatal pneumothorax	1	1	1				
Neonatal respiratory acidosis	1	1	1				
Neonatal respiratory distress	1	1	1				
Nocturnal dyspnoea	13	5	5	8	8		
Obliterative bronchiolitis	1	1	1				
Obstructive airways disorder	74	59	59	15	15		
Organising pneumonia	9	9	9				
Oropharyngeal blistering	24	23	23	1	1		
Oropharyngeal cobble stone mucosa	1			1	1		
Oropharyngeal discomfort	960	418	418	542	542		
Oropharyngeal oedema	14	11	11	3	3		
Oropharyngeal pain	6479	1207	1207	5268	5272	10	10
Oropharyngeal plaque	6	3	3	3	3		
Oropharyngeal spasm	8	8	8				
Oropharyngeal swelling	13	6	6	7	7		
Orthopnoea	27	20	20	7	7		
Painful respiration	137	69	69	68	68		
Paranasal cyst	1			1	1		
Paranasal sinus discomfort	100	19	19	81	81		

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System Organ Class

Respiratory, thoracic and mediastinal disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Paranasal sinus haemorrhage	1			1	1		
Paranasal sinus hypersecretion	17	2	2	15	15		
Paranasal sinus hyposecretion	1			1	1		
Paranasal sinus inflammation	2	1	1	1	1		
Pharyngeal cyst	2	2	2				
Pharyngeal disorder	26	8	8	18	18		
Pharyngeal enanthema	3	1	1	2	2		
Pharyngeal erosion	1			1	1		
Pharyngeal erythema	75	20	20	55	55		
Pharyngeal haemorrhage	6	6	6				
Pharyngeal hypoaesthesia	96	38	38	57	58		
Pharyngeal inflammation	38	16	16	22	22		
Pharyngeal lesion	2			2	2		
Pharyngeal leukoplakia	1			1	1		
Pharyngeal mass	17	6	6	11	11		
Pharyngeal oedema	130	86	86	44	44	1	1
Pharyngeal paraesthesia	229	91	91	135	138		
Pharyngeal stenosis	10	9	9	1	1		
Pharyngeal swelling	860	426	427	430	433	1	1
Pharyngeal ulceration	17	8	8	9	9		
Pleural effusion	156	129	129	27	27	3	3
Pleural rub	1			1	1		
Pleurisy	56	43	43	13	13		
Pleuritic pain	57	28	28	29	29		
Pneumomediastinum	1	1	1				
Pneumonia aspiration	125	125	125				
Pneumonitis	66	56	56	10	10		

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System Organ Class

Respiratory, thoracic and mediastinal disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Pneumothorax	25	25	25			1	1
Pneumothorax spontaneous	5	5	5				
Productive cough	416	159	159	257	257	1	1
Prolonged expiration	4	2	2	2	2		
Pulmonary air leakage	1			1	1		
Pulmonary alveolar haemorrhage	6	6	6				
Pulmonary arterial hypertension	9	9	9				
Pulmonary artery dilatation	2	2	2				
Pulmonary artery occlusion	1	1	1				
Pulmonary artery thrombosis	12	12	12				
Pulmonary calcification	1			1	1		
Pulmonary cavitation	1	1	1				
Pulmonary congestion	56	56	56				
Pulmonary embolism	1736	1731	1731	5	5	9	9
Pulmonary fibrosis	20	20	20				
Pulmonary haemorrhage	9	9	9				
Pulmonary hypertension	21	21	21			2	2
Pulmonary hypertensive crisis	1	1	1				
Pulmonary hypoperfusion	2	2	2				
Pulmonary infarction	55	55	55				
Pulmonary mass	16	9	9	7	7		
Pulmonary microemboli	1	1	1				
Pulmonary necrosis	1	1	1				
Pulmonary oedema	150	149	149	1	1	1	1
Pulmonary pain	208	88	88	120	120		
Pulmonary sarcoidosis	3	2	2	1	1		
Pulmonary sensitisation	2	1	1	1	1		

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System Organ Class

Respiratory, thoracic and mediastinal disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Pulmonary thrombosis	113	111	111	2	2	1	1
Pulmonary vasculitis	2	2	2				
Pulmonary venous thrombosis	1	1	1				
Rales	61	41	41	20	20		
Respiration abnormal	114	46	46	68	68		
Respiratory acidosis	22	19	19	3	3		
Respiratory alkalosis	15	11	11	4	4		
Respiratory arrest	111	109	109	2	2	1	1
Respiratory depression	15	15	15				
Respiratory depth decreased	3	1	1	2	2		
Respiratory disorder	328	196	196	132	132		
Respiratory disorder neonatal	1	1	1				
Respiratory distress	1173	1096	1096	77	77	1	1
Respiratory failure	277	272	272	5	5	1	1
Respiratory fatigue	22	12	12	10	10		
Respiratory muscle weakness	2	2	2				
Respiratory paralysis	1	1	1				
Respiratory symptom	71	28	28	43	43	1	1
Respiratory tract congestion	63	13	13	50	50		
Respiratory tract haemorrhage	4	3	3	1	1		
Respiratory tract inflammation	4	2	2	2	2		
Respiratory tract irritation	23	7	7	16	16		
Respiratory tract oedema	35	35	35				
Restrictive pulmonary disease	1	1	1				
Reversible airways obstruction	1	1	1				
Rhinalgia	64	11	11	52	53		
Rhinitis allergic	36	8	8	28	28		

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System Organ Class

Respiratory, thoracic and mediastinal disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Rhinitis perennial	1			1	1		
Rhinorrhoea	3970	471	471	3499	3499	5	5
Rhonchi	12	7	7	5	5		
Sinonasal obstruction	11	4	4	7	7		
Sinus congestion	115	29	29	85	86		
Sinus disorder	124	18	18	106	106		
Sinus pain	209	87	87	122	122		
Sleep apnoea syndrome	24	13	13	11	11		
Sneezing	736	147	147	588	589	2	2
Snoring	19	9	9	10	10		
Sputum discoloured	31	15	15	16	16		
Sputum increased	12	7	7	5	5		
Sputum retention	7	4	4	3	3		
Status asthmaticus	4	4	4				
Stertor	4	4	4				
Stridor	98	72	72	26	26		
Suffocation feeling	90	44	44	46	46		
Tachypnoea	284	166	167	117	117		
Throat clearing	31	11	12	19	19		
Throat irritation	1262	381	383	875	879	3	3
Throat lesion	3			3	3		
Throat tightness	1289	643	646	641	643	4	4
Tonsillar cyst	1			1	1		
Tonsillar disorder	16	5	5	11	11		
Tonsillar erythema	7	3	3	4	4		
Tonsillar haemorrhage	1	1	1				
Tonsillar hypertrophy	95	28	28	67	67		

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* AE=Adverse Event
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System Organ Class

Respiratory, thoracic and mediastinal disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Tonsillar inflammation	17	3	3	14	14		
Tonsillar ulcer	3	1	1	2	2		
Tonsillolith	2			2	2		
Tracheal compression	1	1	1				
Tracheal disorder	1	1	1				
Tracheal inflammation	2			2	2		
Tracheal oedema	2	2	2				
Tracheal pain	8	2	2	6	6		
Tracheal stenosis	6	6	6				
Tracheomalacia	1		1				
Upper-airway cough syndrome	52	11	11	40	41		
Upper airway obstruction	12	11	11	1	1		
Upper respiratory tract congestion	76	10	10	66	66		
Upper respiratory tract inflammation	8	2	2	6	6		
Upper respiratory tract irritation	3	1	1	2	2		
Use of accessory respiratory muscles	25	17	17	8	8		
Vasomotor rhinitis	1			1	1		
Vocal cord atrophy	1	1	1				
Vocal cord disorder	9	7	7	2	2		
Vocal cord dysfunction	3	2	2	1	1		
Vocal cord inflammation	3	1	1	2	2		
Wheezing	791	434	436	353	355		
Yawning	44	19	19	25	25		
Total:	52347	21811	21842	30470	30505	121	121

System Organ Class

Skin and subcutaneous tissue disorders

Spontaneous	Non Interventional Study

* I=Interval, C=Cumulative
* AE=Adverse Event
* Multiple adverse events coding to the same Preferred Term may have been reported in some cases. Counts are provided for the number of unique Preferred Terms reported.

System Organ Class

Skin and subcutaneous tissue disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Acne	149	26	26	123	123		
Acne cystic	3	1	1	2	2		
Acquired epidermolysis bullosa	1	1	1				
Actinic keratosis	1			1	1		
Acute cutaneous lupus erythematosus	1	1	1				
Acute febrile neutrophilic dermatosis	8	8	8				
Acute generalised exanthematous pustulosis	6	6	6				
Adiposis dolorosa	1	1	1				
Alopecia	214	71	71	143	143		
Alopecia areata	17	7	7	10	10		
Alopecia totalis	1	1	1				
Alopecia universalis	2			2	2		
Androgenetic alopecia	2	2	2				
Angioedema	749	731	731	18	18		
Angiokeratoma	1			1	1		
Angiolymphoid hyperplasia with eosinophilia	1			1	1		
Anhidrosis	1	1	1				
Argyria	1			1	1		
Blister	676	226	226	450	450	1	1
Blister rupture	4			4	4		
Blood blister	46	21	21	25	25		
Brachioradial pruritus	1			1	1		
Brow ptosis	1			1	1		
Bullous haemorrhagic dermatosis	1	1	1				
Butterfly rash	14	5	5	9	9		
Capillaritis	3			3	3		
Chloasma	1			1	1		

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* AE=Adverse Event
* Multiple adverse events coding to the same Preferred Term may have been reported in some cases. Counts are provided for the number of unique Preferred Terms reported.

System Organ Class

Skin and subcutaneous tissue disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Chronic pigmented purpura	1			1	1		
Chronic spontaneous urticaria	4	2	2	2	2		
Circumoral oedema	19	7	7	12	12	1	1
Circumoral swelling	22	8	8	14	14		
Cold sweat	1182	479	480	697	702		
Cold urticaria	6			6	6		
Cutaneous lupus erythematosus	2	2	2				
Cutaneous sarcoidosis	4	4	4				
Cutaneous symptom	12	9	9	3	3		
Cutaneous vasculitis	43	40	40	3	3		
Dandruff	3			3	3		
Decubitus ulcer	14	7	7	7	7		
Dermal cyst	12	3	3	9	9		
Dermatitis	207	63	63	144	144		
Dermatitis acneiform	25	2	2	23	23		
Dermatitis allergic	337	134	135	202	202	1	1
Dermatitis atopic	47	14	14	33	33		
Dermatitis bullous	61	60	60	1	1	1	1
Dermatitis contact	44	9	9	35	35		
Dermatitis diaper	3	1	1	2	2		
Dermatitis exfoliative	8	7	7	1	1		
Dermatitis exfoliative generalised	10	10	10				
Dermatitis herpetiformis	5	2	2	3	3		
Dermatitis psoriasiform	10	3	3	7	7		
Dermatomyositis	13	13	13				
Dermatosis	14	2	2	12	12		
Diabetic wound	1	1	1				

* I=Interval, C=Cumulative
* AE=Adverse Event
* Multiple adverse events coding to the same Preferred Term may have been reported in some cases. Counts are provided for the number of unique Preferred Terms reported.

System Organ Class

Skin and subcutaneous tissue disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Diffuse alopecia	3	1	1	2	2		
Drug eruption	95	44	44	50	51		
Drug reaction with eosinophilia and systemic symptoms	7	7	7				
Dry skin	302	87	87	215	215	1	1
Dyshidrotic eczema	19	8	8	11	11		
Ecchymosis	93	31	31	62	62		
Eczema	403	121	121	282	282	1	1
Eczema asteatotic	7	2	2	5	5		
Eczema infantile	1			1	1		
Eczema nummular	13	3	3	10	10		
Eczema vesicular	1	1	1				
Eczema weeping	2			2	2		
Eosinophilic pustular folliculitis	1			1	1		
Ephelides	2			2	2		
Epidermal necrosis	1	1	1				
Erythema	7887	1880	1883	5995	6004	12	12
Erythema ab igne	1			1	1		
Erythema annulare	5	3	3	2	2		
Erythema marginatum	1			1	1		
Erythema multiforme	80	75	75	5	5		
Erythema nodosum	55	30	30	25	25		
Erythematotelangiectatic rosacea	1			1	1		
Erythrodermic psoriasis	1			1	1		
Erythrosis	2			2	2		
Excessive granulation tissue	1	1	1				
Exfoliative rash	24	15	15	9	9		
Fingerprint loss	1			1	1		

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System Organ Class

Skin and subcutaneous tissue disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Fixed eruption	4			4	4		
Follicular eczema	1	1	1				
Fracture blisters	1			1	1		
Granuloma annulare	4	2	2	2	2		
Granuloma skin	3	1	1	2	2		
Guttate psoriasis	11	5	5	6	6		
Haemorrhage subcutaneous	63	61	61	2	2		
Haemorrhagic urticaria	1	1	1				
Haemosiderin stain	1			1	1		
Hair colour changes	5	1	1	4	4		
Hair disorder	8			8	8		
Hair growth abnormal	4			4	4		
Hair texture abnormal	9	4	4	5	5		
Hand dermatitis	11	1	1	10	10		
Henoch-Schonlein purpura	23	15	15	8	8		
Hidradenitis	6	2	2	4	4		
Hirsutism	2	1	1	1	1		
Hyperhidrosis	5023	1458	1460	3558	3563	6	6
Hyperkeratosis	1			1	1		
Hypersensitivity vasculitis	17	17	17				
Hypertrichosis	1			1	1		
Idiopathic angioedema	3	3	3				
Idiopathic urticaria	3	1	1	2	2		
Ingrowing nail	2			2	2		
Ingrown hair	1	1	1				
Intertrigo	2			2	2		
Itching scar	7	2	2	5	5		

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System Organ Class

Skin and subcutaneous tissue disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Keloid scar	1			1	1		
Keratolysis exfoliativa acquired	2			2	2		
Keratosis pilaris	8	1	1	7	7		
Koebner phenomenon	1			1	1		
Lentigo	1			1	1		
Leukoplakia	2	1	1	1	1		
Lichenification	2			2	2		
Lichenoid keratosis	8	4	4	4	4		
Lichen planus	14	5	5	9	9		
Lichen sclerosus	7	3	3	4	4		
Linear IgA disease	1	1	1				
Lipoatrophy	1			1	1		
Lipodystrophy acquired	2	2	2				
Livedo reticularis	86	33	33	53	53	1	1
Lividity	13	10	10	3	3		
Macule	36	7	7	29	29		
Madarosis	8	7	7	1	1		
Mechanical urticaria	37	10	10	27	27	2	2
Mechanic's hand	1	1	1				
Miliaria	86	26	27	59	59		
Mucocutaneous disorder	1			1	1		
Mucocutaneous rash	1	1	1				
Mucocutaneous ulceration	1	1	1				
Nail bed bleeding	1			1	1		
Nail discolouration	24	6	6	18	18		
Nail disorder	2			2	2		
Nail pigmentation	2	2	2				

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System Organ Class

Skin and subcutaneous tissue disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Nail ridging	1	1	1				
Needle track marks	1			1	1		
Neurodermatitis	12			12	12		
Neutrophilic dermatosis	3	3	3				
Night sweats	870	239	239	629	631	3	3
Nodular rash	2			2	2		
Oculomucocutaneous syndrome	22	20	20	2	2		
Oedema blister	1	1	1				
Onychalgia	6	1	1	5	5		
Onychoclasis	6	1	1	5	5		
Onycholysis	3			3	3		
Onychomadesis	2	1	1	1	1		
Pain of skin	526	172	172	354	354	1	1
Palmar erythema	41	15	15	25	26		
Palmar-plantar erythrodysaesthesia syndrome	6	1	1	5	5		
Palmoplantar pustulosis	3	2	2	1	1		
Palpable purpura	5	3	3	2	2		
Panniculitis	7	7	7				
Papule	133	34	34	99	99		
Paraneoplastic dermatomyositis	1	1	1				
Parapsoriasis	2	1	1	1	1		
Pathergy reaction	1			1	1		
Peau d'orange	3			3	3		
Pemphigoid	42	42	42				
Pemphigus	18	18	18				
Penile ulceration	2			2	2		
Perioral dermatitis	4	1	1	3	3		

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System Organ Class

Skin and subcutaneous tissue disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Perivascular dermatitis	2			2	2		
Pernio-like erythema	6	1	1	5	5		
Petechiae	382	167	167	215	215	1	1
Photosensitivity reaction	145	48	48	97	97	1	1
Pigmentation disorder	36	6	6	30	30		
Piloerection	59	19	19	39	40		
Pityriasis	14	4	4	10	10		
Pityriasis lichenoides et varioliformis acuta	3	1	1	2	2		
Pityriasis rosea	103	24	24	79	79		
Plantar erythema	7	2	2	5	5		
Poikiloderma	1			1	1		
Polymorphic light eruption	1			1	1		
Post inflammatory pigmentation change	1			1	1		
Progressive macular hypomelanosis	1	1	1				
Prurigo	20	3	3	17	17		
Pruritus	11303	2768	2771	8519	8532	12	12
Pruritus allergic	9	4	4	5	5		
Pseudofolliculitis	4	1	1	3	3		
Psoriasis	170	56	56	114	114	1	1
Purpura	193	72	72	121	121	2	2
Pustular psoriasis	4	2	2	2	2		
Pyoderma gangrenosum	1	1	1				
Rash	10669	2702	2708	7946	7961	12	12
Rash erythematous	1583	507	511	1070	1072	4	4
Rash macular	970	235	236	731	734	1	1
Rash maculo-papular	258	85	85	173	173		
Rash maculovesicular	3	1	1	2	2		

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System Organ Class

Skin and subcutaneous tissue disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Rash morbilliform	70	25	25	45	45		
Rash neonatal	3			3	3		
Rash papular	470	126	126	344	344		
Rash papulosquamous	3			3	3		
Rash pruritic	1861	506	506	1354	1355		
Rash rubelliform	3	3	3				
Rash scarlatiniform	2			2	2		
Rash vesicular	178	50	50	128	128		
Red man syndrome	2	1	1	1	1		
Rosacea	32	10	10	22	22		
Scab	70	13	13	57	57		
Scar pain	16	3	3	13	13		
Scleroderma associated digital ulcer	1	1	1				
Seborrhoea	4	1	1	3	3		
Seborrhoeic dermatitis	8	3	3	5	5		
Sensitive skin	7434	291	291	7143	7143		
Skin atrophy	3	1	1	2	2		
Skin burning sensation	447	116	116	331	331	2	2
Skin depigmentation	10	4	4	6	6		
Skin discharge	3	2	2	1	1		
Skin discolouration	406	111	112	293	294		
Skin discomfort	25	3	3	22	22		
Skin disorder	298	94	94	204	204		
Skin erosion	20	8	8	12	12		
Skin exfoliation	214	68	68	146	146		
Skin fissures	21	7	7	14	14		
Skin haemorrhage	51	17	17	34	34		

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System Organ Class

Skin and subcutaneous tissue disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Skin hyperpigmentation	11	1	1	10	10		
Skin hypertrophy	13	4	4	9	9		
Skin hypopigmentation	2			2	2		
Skin indentation	6			6	6		
Skin induration	21	4	4	17	17		
Skin irritation	180	43	43	137	137		
Skin laxity	4	1	1	3	3		
Skin lesion	188	54	54	134	134	1	1
Skin lesion inflammation	1	1	1				
Skin mass	70	15	15	55	55		
Skin necrosis	7	7	7				
Skin odour abnormal	24	7	7	17	17		
Skin oedema	13	1	1	12	12		
Skin plaque	21	6	6	15	15		
Skin reaction	292	62	62	230	230		
Skin sensitisation	85	12	12	73	73		
Skin striae	8	3	3	5	5		
Skin swelling	136	30	30	106	106		
Skin texture abnormal	4	1	1	3	3		
Skin tightness	84	30	30	54	54		
Skin ulcer	39	20	20	19	19		
Skin warm	263	93	94	169	169	1	1
Skin weeping	13	9	9	4	4		
Skin wrinkling	15	4	4	11	11		
Solar dermatitis	3	2	2	1	1		
Solar lentigo	3	3	3				
Solar urticaria	5	1	1	4	4		

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System Organ Class

Skin and subcutaneous tissue disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Splinter haemorrhages	2	1	1	1	1		
Stasis dermatitis	2			2	2		
Stevens-Johnson syndrome	25	24	24	1	1		
Sticky skin	3			3	3		
Subcutaneous emphysema	1	1	1				
Sweat gland disorder	1			1	1		
Symmetrical drug-related intertriginous and flexural exanther	2	2	2				
Systemic lupus erythematosus rash	8	6	6	2	2		
Target skin lesion	2	2	2				
Telangiectasia	7	3	3	4	4		
Toxic epidermal necrolysis	7	7	7			1	1
Toxic skin eruption	36	35	35	1	1		
Transient acantholytic dermatosis	1			1	1		
Trichodynia	5	1	1	4	4		
Trichorrhexis	1			1	1		
Umbilical haematoma	1	1	1				
Urticaria	5480	1664	1665	3806	3815	6	6
Urticaria cholinergic	3			3	3		
Urticaria chronic	18	12	12	6	6		
Urticaria contact	1	1	1				
Urticarial dermatitis	2			2	2		
Urticarial vasculitis	6	6	6				
Urticaria papular	13	5	5	8	8		
Urticaria physical	3			3	3		
Urticaria pressure	1	1	1				
Urticaria thermal	5			5	5		
Urticaria vesiculosa	1	1	1				

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System Organ Class

Skin and subcutaneous tissue disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Vascular purpura	25	18	18	7	7		
Vascular skin disorder	1	1	1				
Vasculitic rash	25	8	8	17	17		
Vitiligo	5	1	1	4	4		
Yellow skin	31	12	12	19	19		
Total:	65151	16965	16990	48093	48161	76	76

System Organ Class

Social circumstances

Preferred Term	*Total # of Spontaneous AE*	Spontaneous			
		Serious		Nonserious	
		I	C	I	C
Aborted pregnancy	1	1	1		
Bedridden	221	68	68	153	153
Breast feeding	12	1	1	11	11
Breast prosthesis user	1			1	1
Caffeine consumption	1			1	1
Caregiver	1			1	1
Contraindication to medical treatment	2			2	2
Contraindication to vaccination	37			37	37
Dependence on oxygen therapy	1	1	1		
Disability	17	14	14	3	3
Drug abuser	1	1	1		
Excessive exercise	1	1	1		
Exercise lack of	1			1	1
Fasting	2			2	2
Hair dye user	2	1	1	1	1
Hearing disability	7	3	3	4	4

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System Organ Class

Social circumstances

Preferred Term	*Total # of Spontaneous AE*	Spontaneous			
		Serious		Nonserious	
		I	C	I	C
Housebound	2			2	2
Illiteracy	1	1	1		
Immobile	37	37	37		
Immobilisation prolonged	1	1	1		
Impaired driving ability	73	32	32	41	41
Impaired quality of life	33	15	15	18	18
Impaired work ability	314	152	152	162	162
Job dissatisfaction	4	1	1	3	3
Joint prosthesis user	1	1	1		
Loss of personal independence in daily activities	699	263	264	435	435
Marital problem	1			1	1
Menopause	15	5	5	10	10
Non-tobacco user	1			1	1
Overwork	1			1	1
Partner stress	1			1	1
Patient dissatisfaction with treatment	1			1	1
Patient uncooperative	2	1	1	1	1
Physical disability	8	4	4	4	4
Planning to become pregnant	2			2	2
Postmenopause	2	2	2		
Primigravida	1	1	1		
Sick relative	1	1	1		
Sight disability	6	3	3	3	3
Sitting disability	20	7	7	13	13
Social problem	1			1	1
Tanning	2			2	2
Tobacco user	1			1	1

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System Organ Class

Social circumstances

Preferred Term		*Total # of Spontaneous AE*	Spontaneous			
			Serious		Nonserious	
			I	C	I	C
Urinary assistance device user		1			1	1
Walking aid user		16	3	3	13	13
Walking disability		41	15	15	26	26
Water pollution		5	3	3	2	2
Wheelchair user		4	1	1	3	3
	Total:	1606	640	641	965	965

System Organ Class

SOC Not Yet Coded

Preferred Term		*Total # of Spontaneous AE*	Spontaneous	
			Nonserious	
			I	C
		35	35	35
	Total:	35	35	35

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* AE=Adverse Event
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System Organ Class

Surgical and medical procedures

Preferred Term	*Total # of Spontaneous AE*	Spontaneous			
		Serious		Nonserious	
		I	C	I	C
Abdominal operation	1			1	1
Abortion induced	3	2	2	1	1
Abscess drainage	2	1	1	1	1
Airway secretion clearance therapy	1	1	1		
Analgesic therapy	2			2	2
Anaphylaxis prophylaxis	1	1	1		
Antacid therapy	1			1	1
Antiallergic therapy	1			1	1
Anticoagulant therapy	1			1	1
Appendicectomy	1	1	1		
Asthma prophylaxis	3	2	2	1	1
Axillary lymphadenectomy	6	3	3	3	3
Bed rest	16	3	3	13	13
Cardiac ablation	1	1	1		
Cardiac pacemaker insertion	1	1	1		
Cardioversion	1			1	1
Catheter placement	1	1	1		
Central nervous system stimulation	1	1	1		
Chemotherapy	1			1	1
Contraceptive diaphragm	1			1	1
Cooling therapy	1			1	1
COVID-19 immunisation	26	14	14	12	12
Cranial nerve decompression	1	1	1		
Dental care	1			1	1
Dermabrasion	1			1	1
Dermal filler injection	1			1	1
Diabetic diet	1	1	1		

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System Organ Class

Surgical and medical procedures

Preferred Term	*Total # of Spontaneous AE*	Spontaneous			
		Serious		Nonserious	
		I	C	I	C
Drainage	7			7	7
Emergency care	2	1	1	1	1
Empyema drainage	1	1	1		
Endodontic procedure	1			1	1
Endometrial scratching	1			1	1
Endotracheal intubation	1	1	1		
Fluid replacement	1			1	1
Gastrointestinal surgery	1	1	1		
Haematoma evacuation	1	1	1		
Haemodialysis	1			1	1
Hernia repair	2	2	2		
Hip arthroplasty	1			1	1
Home care	1	1	1		
Hospitalisation	8	8	8		
Hysterectomy	2	1	1	1	1
Ileectomy	1	1	1		
Immune tolerance induction	1			1	1
Immunisation	12	2	2	10	10
Immunosuppressant drug therapy	1			1	1
Influenza immunisation	1			1	1
Infusion	2			2	2
Injection	3			3	3
Interchange of vaccine products	2			2	2
Intra-cerebral aneurysm operation	1	1	1		
Joint stabilisation	2	1	1	1	1
Knee arthroplasty	3	1	1	2	2
Knee operation	2	1	1	1	1

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System Organ Class

Surgical and medical procedures

Preferred Term	*Total # of Spontaneous AE*	Spontaneous			
		Serious		Nonserious	
		I	C	I	C
Limb immobilisation	22	5	5	17	17
Limb operation	3	1	1	2	2
Local anaesthesia	1			1	1
Localised alternating hot and cold therapy	1	1	1		
Lymphadenectomy	2			2	2
Macrophage activation	1	1	1		
Mass excision	4			4	4
Mechanical ventilation	3	3	3		
Medical diet	1			1	1
Medical induction of coma	1	1	1		
Menstrual cycle management	10			10	10
Migraine prophylaxis	1	1	1		
Mole excision	1			1	1
Multiple sclerosis relapse prophylaxis	2	1	1	1	1
Nail operation	1			1	1
Nephrectomy	1			1	1
Nerve block	1	1	1		
Oxygen therapy	1	1	1		
Palliative care	1	1	1		
Peripheral nerve injection	1			1	1
Physiotherapy	1			1	1
Pleural decortication	1	1	1		
Prophylaxis	1			1	1
Prophylaxis of nausea and vomiting	3	1	1	2	2
Quarantine	2	1	1	1	1
Radiotherapy	1			1	1
Renal transplant	1			1	1

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System Organ Class

Surgical and medical procedures

Preferred Term	*Total # of Spontaneous AE*	Spontaneous			
		Serious		Nonserious	
		I	C	I	C
Resuscitation	7	7	7		
Self-medication	2			2	2
Sinus operation	1			1	1
Skin lesion removal	1			1	1
Small intestinal resection	1	1	1		
Spinal fusion surgery	1	1	1		
Splenic artery embolisation	1	1	1		
Surgery	3	1	1	2	2
Tetanus immunisation	1			1	1
Therapeutic procedure	1			1	1
Therapy cessation	1			1	1
Therapy change	1			1	1
Therapy interrupted	1			1	1
Thrombectomy	1	1	1		
Thrombolysis	3	3	3		
Thyroidectomy	1			1	1
Tooth extraction	9	1	1	8	8
Tooth repair	1			1	1
Transfusion	1	1	1		
Tumour excision	1			1	1
Vagotomy	1	1	1		
Vascular anastomosis	1	1	1		
Venous arterialisation	1	1	1		
Weight loss diet	1	1	1		
Wheat-free diet	1	1	1		
Wisdom teeth removal	2			2	2
Wound closure	1			1	1

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* AE=Adverse Event
* Multiple adverse events coding to the same Preferred Term may have been reported in some cases. Counts are provided for the number of unique Preferred Terms reported.

System Organ Class

Surgical and medical procedures

Preferred Term	*Total # of Spontaneous AE*	Spontaneous			
		Serious		Nonserious	
		I	C	I	C
Wound drainage	1	1	1		
Total:	257	101	101	156	156

System Organ Class

Vascular disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Accelerated hypertension	4			4	4		
Achenbach syndrome	2			2	2		
Acute aortic syndrome	2	2	2				
Air embolism	1	1	1				
Aneurysm	20	17	17	3	3		
Aneurysm ruptured	12	12	12				
Angiopathy	19	7	7	12	12		
Aortic aneurysm	14	13	13	1	1		
Aortic aneurysm rupture	12	12	12				
Aortic arteriosclerosis	16	8	8	8	8		
Aortic dilatation	3	2	2	1	1		
Aortic disorder	3	3	3				
Aortic dissection	28	28	28				
Aortic elongation	2			2	2		
Aortic embolus	2	2	2				
Aortic rupture	2	2	2				
Aortic stenosis	8	8	8				
Aortic thrombosis	3	3	3				
Aortitis	3	3	3				
Arterial disorder	6	4	4	2	2		

* I=Interval, C=Cumulative
* AE=Adverse Event
* Multiple adverse events coding to the same Preferred Term may have been reported in some cases. Counts are provided for the number of unique Preferred Terms reported.

System Organ Class

Vascular disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Arterial haemorrhage	2	1	1	1	1		
Arterial occlusive disease	19	17	17	2	2		
Arterial rupture	3	3	3				
Arterial stenosis	6	6	6				
Arterial stiffness	1			1	1		
Arterial thrombosis	24	23	23	1	1	1	1
Arteriosclerosis	40	31	31	9	9		
Arteriovenous fistula	2	2	2				
Arteritis	3	3	3				
Artery dissection	4	4	4				
Atheroembolism	1	1	1				
Axillary vein thrombosis	6	4	4	2	2		
Behcet's syndrome	7	7	7				
Bleeding varicose vein	2	2	2				
Blood pressure fluctuation	206	72	72	134	134		
Blood pressure inadequately controlled	11	4	4	7	7		
Bloody discharge	9	5	5	4	4		
Blue toe syndrome	19	12	12	7	7		
Brachiocephalic artery stenosis	1	1	1				
Brachiocephalic vein occlusion	1	1	1				
Brachiocephalic vein thrombosis	1	1	1				
Capillary disorder	3			3	3		
Capillary fragility	17	3	3	14	14		
Capillary leak syndrome	2	2	2				
Circulatory collapse	290	286	287	3	3	1	1
Claudication of jaw muscles	2	2	2				
CT hypotension complex	2	2	2				

* I=Interval, C=Cumulative
* AE=Adverse Event
* Multiple adverse events coding to the same Preferred Term may have been reported in some cases. Counts are provided for the number of unique Preferred Terms reported.

System Organ Class

Vascular disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Cyanosis	255	137	137	118	118	1	1
Deep vein thrombosis	1190	1180	1180	10	10	4	4
Dependent rubor	3	1	1	2	2		
Diastolic hypertension	4	3	3	1	1		
Diastolic hypotension	4	3	3	1	1		
Diffuse vasculitis	1	1	1				
Embolism	105	105	105			1	1
Embolism arterial	8	8	8				
Embolism venous	16	16	16				
Endothelial dysfunction	1			1	1		
Erythromelalgia	4	2	2	2	2		
Essential hypertension	11	8	8	3	3	1	1
Extravasation blood	2			2	2		
Extremity necrosis	5	4	4	1	1		
Femoral artery embolism	3	3	3				
Fibromuscular dysplasia	2	2	2				
Flushing	1863	493	499	1354	1364	3	3
Giant cell arteritis	38	35	35	3	3		
Granulomatosis with polyangiitis	1	1	1				
Haematoma	354	132	132	222	222		
Haemodynamic instability	15	12	12	3	3		
Haemorrhage	505	486	486	19	19	4	4
Haemorrhagic infarction	4	4	4				
Hot flush	1896	531	533	1361	1363		
Hyperaemia	67	10	10	56	57		
Hypertension	4996	2314	2318	2678	2678	11	11
Hypertensive crisis	588	579	579	9	9	2	2

* I=Interval, C=Cumulative
* AE=Adverse Event
* Multiple adverse events coding to the same Preferred Term may have been reported in some cases. Counts are provided for the number of unique Preferred Terms reported.

System Organ Class

Vascular disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Hypertensive emergency	20	20	20				
Hypertensive urgency	11	10	10	1	1		
Hypoperfusion	8	6	6	2	2		
Hypotension	1888	911	912	976	976	8	8
Hypotensive crisis	11	11	11				
Hypovolaemic shock	44	43	43	1	1		
Iliac artery occlusion	1	1	1				
Infarction	27	27	27				
Inferior vena caval occlusion	1	1	1				
Intermittent claudication	12	7	7	5	5		
Internal haemorrhage	67	67	67				
Ischaemia	34	31	31	3	3		
Ischaemic limb pain	3	2	2	1	1		
Jugular vein distension	5	3	3	2	2		
Jugular vein thrombosis	21	20	20	1	1		
Kawasaki's disease	3	3	3				
Labile blood pressure	9	6	6	3	3		
Labile hypertension	4	2	2	2	2		
Lymphangiectasia	1	1	1				
Lymphangiopathy	1	1	1				
Lymphocele	5			5	5		
Lymphoedema	223	64	64	159	159	2	2
MAGIC syndrome	1	1	1				
Malignant hypertension	9	9	9				
May-Thurner syndrome	2	2	2				
Microangiopathy	6	2	2	4	4		
Microembolism	5	5	5				

* I=Interval, C=Cumulative
* AE=Adverse Event
* Multiple adverse events coding to the same Preferred Term may have been reported in some cases. Counts are provided for the number of unique Preferred Terms reported.

System Organ Class

Vascular disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Microscopic polyangiitis	3	3	3				
Necrosis ischaemic	1	1	1				
Neurogenic shock	23	23	23				
Obstructive shock	3	3	3				
Orthostatic hypertension	5	4	4	1	1		
Orthostatic hypotension	83	35	35	48	48		
Pallor	918	414	416	502	502	3	3
Pelvic venous thrombosis	20	19	19	1	1		
Peripheral arterial occlusive disease	6	5	5	1	1		
Peripheral artery aneurysm						1	1
Peripheral artery occlusion	6	6	6				
Peripheral artery stenosis	1	1	1				
Peripheral artery thrombosis	31	29	29	2	2		
Peripheral circulatory failure	40	12	13	27	27		
Peripheral coldness	850	288	289	558	561	3	3
Peripheral embolism	18	17	17	1	1		
Peripheral ischaemia	56	42	42	14	14		
Peripheral vascular disorder	117	31	31	86	86	1	1
Peripheral vein stenosis	2	2	2				
Peripheral vein thrombus extension	1	1	1				
Peripheral venous disease	37	14	14	23	23		
Periphlebitis	2			2	2		
Phlebitis	106	60	60	46	46		
Phlebitis deep	2	2	2				
Phlebitis superficial	31	14	14	17	17		
Poor peripheral circulation	40	15	15	25	25		
Poor venous access	5	1	1	4	4	1	1

* I=Interval, C=Cumulative
* AE=Adverse Event
* Multiple adverse events coding to the same Preferred Term may have been reported in some cases. Counts are provided for the number of unique Preferred Terms reported.

System Organ Class

Vascular disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Post thrombotic syndrome	3	3	3				
Prehypertension	3			3	3		
Pseudovasculitis	1			1	1		
Raynaud's phenomenon	124	42	42	82	82		
Secondary hypertension	6	2	2	4	4		
Shock	116	113	113	3	3	1	1
Shock haemorrhagic	7	7	7				
Shock symptom	12	11	11	1	1		
Spider vein	3			3	3		
Subclavian artery thrombosis	2	2	2				
Subclavian vein occlusion	1	1	1				
Subclavian vein stenosis	1	1	1				
Subclavian vein thrombosis	18	18	18				
Superficial vein prominence	5	2	2	3	3		
Superior vena cava syndrome	1	1	1				
Systolic hypertension	16	9	9	7	7		
Takayasu's arteritis	2	2	2				
Thromboangiitis obliterans	2	1	1	1	1		
Thrombophlebitis	152	101	101	51	51		
Thrombophlebitis superficial	206	151	151	55	55	1	1
Thrombosed varicose vein	5	2	2	3	3		
Thrombosis	1020	999	999	21	21	8	8
Varicophlebitis	7	5	5	2	2		
Varicose ulceration	2	1	1	1	1		
Varicose vein	43	15	15	28	28		
Varicose vein ruptured	1			1	1		
Vascular calcification	2	1	1	1	1		

* I=Interval, C=Cumulative
* AE=Adverse Event
* Multiple adverse events coding to the same Preferred Term may have been reported in some cases. Counts are provided for the number of unique Preferred Terms reported.

System Organ Class

Vascular disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Vascular compression	1	1	1				
Vascular fragility	1			1	1		
Vascular insufficiency	1	1	1				
Vascular occlusion	5	5	5				
Vascular pain	39	12	12	27	27		
Vascular rupture	8	3	3	5	5		
Vascular stenosis	3	3	3				
Vasculitis	124	69	69	55	55		
Vasculitis necrotising	5	4	4	1	1		
Vasoconstriction	20	9	9	11	11		
Vasodilatation	51	24	24	27	27		
Vasospasm	7	3	3	4	4		
Vein collapse	2	1	1	1	1		
Vein discolouration	10	1	1	9	9		
Vein disorder	48	12	12	36	36		
Vein rupture	7	7	7				
Vein wall hypertrophy	1	1	1				
Vena cava embolism	2	2	2				
Vena cava thrombosis	9	9	9				
Venous haemorrhage	3	3	3				
Venous occlusion	5	5	5				
Venous thrombosis	76	70	70	6	6		
Venous thrombosis in pregnancy	1	1	1				
Venous thrombosis limb	106	92	92	14	14	2	2
Vessel perforation	1			1	1		
White coat hypertension	4	1	1	3	3		
Withdrawal hypertension	5	2	2	3	3		

* I=Interval, C=Cumulative
* AE=Adverse Event
* Multiple adverse events coding to the same Preferred Term may have been reported in some cases. Counts are provided for the number of unique Preferred Terms reported.

System Organ Class

Vascular disorders

Preferred Term	*Total # of Spontaneous AE*	Spontaneous				Non Interventional Study	
		Serious		Nonserious		Serious	
		I	C	I	C	I	C
Total:	19922	10821	10839	9067	9083	60	60

* I=Interval, C=Cumulative
* AE=Adverse Event
* Multiple adverse events coding to the same Preferred Term may have been reported in some cases. Counts are provided for the number of unique Preferred Terms reported.

Appendix 2.3 Cumulative Summary Tabulation of Demographic Data (S6.1)
BNT162/PF-07302048
Cumulative demographic information entered into the database through 18-JUN-2021

	BNT162b1 (N=195)	BNT162b2 (N=23248)	BNT162b2 & Blinded boost (N=869)	Placebo to BNT162b2 (N=21235)
Age (years)				
<=17	0	1933 (8.3)	0	1257 (5.9)
18-30	39 (20.0)	3087 (13.3)	161 (18.5)	2551 (12.0)
31-50	48 (24.6)	7465 (32.1)	469 (54.0)	6975 (32.8)
51-64	18 (9.2)	6290 (27.1)	202 (23.2)	6177 (29.1)
65-74	81 (41.5)	3573 (15.4)	30 (3.5)	3446 (16.2)
>=75	9 (4.6)	900 (3.9)	7 (0.8)	829 (3.9)
UNSPECIFIED	0	0	0	0
Mean	51.90	46.85	43.04	48.31
Median (range)	53.00 (19- 82)	49.00 (0- 89)	44.00 (18- 82)	50.00 (12- 91)
Race, n (%)				
WHITE	177 (90.8)	19096 (82.1)	694 (79.9)	17607 (82.9)
BLACK	6 (3.1)	1962 (8.4)	78 (9.0)	1824 (8.6)
ASIAN	12 (6.2)	1247 (5.4)	69 (7.9)	933 (4.4)
HISPANIC	0	156 (0.7)	8 (0.9)	156 (0.7)
OTHER	0	756 (3.3)	17 (2.0)	677 (3.2)
UNSPECIFIED	0	31 (0.1)	3 (0.3)	38 (0.2)
Gender, n (%)				
MALE	83 (42.6)	11891 (51.1)	425 (48.9)	10667 (50.2)
FEMALE	112 (57.4)	11357 (48.9)	444 (51.1)	10568 (49.8)

Study C4591015 enrolled pregnant women and their infants. Infant participants were not vaccinated with the study investigational product
Includes Protocols: C4591001,C4591005,C4591007,C4591015,C4591017,C4591020
PFIZER CONFIDENTIAL Date of Generation: 03JUL2021 (11:16)

Appendix 2.3 Cumulative Summary Tabulation of Demographic Data (S6.1)
BNT162/PF-07302048
Cumulative demographic information entered into the database through 18-JUN-2021

	BNT162b2SA (N=330)	Blinded Therapy (N=4757)	Placebo (N=1154)	Total (N=51788)
Age (years)				
<=17	0	2501 (52.6)	118 (10.2)	5809 (11.2)
18-30	120 (36.4)	710 (14.9)	187 (16.2)	6855 (13.2)
31-50	177 (53.6)	959 (20.2)	368 (31.9)	16461 (31.8)
51-64	33 (10.0)	438 (9.2)	279 (24.2)	13437 (25.9)
65-74	0	113 (2.4)	152 (13.2)	7395 (14.3)
>=75	0	36 (0.8)	50 (4.3)	1831 (3.5)
UNSPECIFIED	0	0	0	0
Mean	35.76	23.74	44.76	45.16
Median (range)	36.00 (18- 55)	14.00 (0- 86)	45.00 (12- 85)	47.00 (0- 91)
Race, n (%)				
WHITE	258 (78.2)	3658 (76.9)	839 (72.7)	42329 (81.7)
BLACK	40 (12.1)	580 (12.2)	182 (15.8)	4672 (9.0)
ASIAN	26 (7.9)	246 (5.2)	99 (8.6)	2632 (5.1)
HISPANIC	3 (0.9)	76 (1.6)	12 (1.0)	411 (0.8)
OTHER	3 (0.9)	184 (3.9)	21 (1.8)	1658 (3.2)
UNSPECIFIED	0	13 (0.3)	1 (<0.1)	86 (0.2)
Gender, n (%)				
MALE	171 (51.8)	2448 (51.5)	596 (51.6)	26281 (50.7)
FEMALE	159 (48.2)	2309 (48.5)	558 (48.4)	25507 (49.3)

Study C4591015 enrolled pregnant women and their infants. Infant participants were not vaccinated with the study investigational product
Includes Protocols: C4591001,C4591005,C4591007,C4591015,C4591017,C4591020
PFIZER CONFIDENTIAL Date of Generation: 03JUL2021 (11:16)

Appendix 2.3B Cumulative Summary Tabulations of Demographic Data (BNT BNT162-01 and BNT162-04)
BNT162/PF-07302048

	BNT162a1 (N=30)	BNT162b1 (N=120)	BNT162b2 (N=266)	BNT162c2 P/B (N=48)	BNT162c2 SD (N=48)	BNT162b3 (N=96)	TOTAL* (N = 608)
Age [years]							
≥18 to <30 years	4 (13)	23 (19)	28 (11)	16 (33)	20 (42)	19 (20)	110 (18%)
≥30 to <50 years	10 (33)	43 (36)	78 (29)	24 (50)	15 (31)	26 (27)	196 (32%)
≥50 to <65 years	16 (53)	32 (27)	104 (39)	8 (17)	13 (27)	25 (26)	198 (33%)
≥65 to <75 years	0 (0)	20 (17)	50 (19)	0 (0)	0 (0)	20 (21)	90 (15%)
≥75 years	0 (0)	2 (2)	6 (2)	0 (0)	0 (0)	6 (6)	14 (2%)
Race, n (%)							
Asian	0 (0)	2 (2)	2 (0)	1 (2)	1 (2)	1 (1)	7 (1%)
Black or African American	0 (0)	1 (1)	1 (0)	0 (0)	0 (0)	0 (0)	2 (0%)
White	29 (97)	117 (98)	263 (99)	46 (96)	47 (98)	95 (99)	597 (98%)
Other/multiple	1 (3)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	2 (0%)
Hispanic or Latino	0 (0)	2 (2)	1 (0)	2 (4)	1 (2)	0 (0)	6 (1%)
Not Hispanic or Latino	30 (100)	118 (98)	265 (100)	46 (96)	47 (98)	96 (100)	602 (99%)
Gender, n (%)							
Male	18 (60)	57 (48)	134 (50)	24 (50)	18 (38)	42 (44)	293 (48%)
Female	12 (40)	63 (53)	132 (50)	24 (50)	30 (63)	54 (56)	315 (52%)

ND = not determined
*Calculated by adding total exposures by mRNA constructs: BNT162a1 includes 0.1, 0.3, and 3 µg younger dose ranging cohorts; BNT162b1 includes 1, 3, 10, 20, 30, 50, 60 µg younger dose ranging cohorts and 10, 20, 30 µg older dose ranging cohorts; BNT162b2 include 1, 3, 10, 20, 30 µg younger dose ranging cohorts, 10, 20, 30 µg older dose ranging cohorts, and 3-30 µg expansion cohorts (including cohort 14); BNT162c2 P/B includes 0.1, 0.3, 1, 3 µg younger dose ranging cohorts; BNT162c2 SD includes 0.1, 0.3, 0.6, 1 µg younger dose ranging cohorts; BNT162b3 include 3, 10, 20, 30 µg younger dose ranging cohorts and 3, 10, 20, 30 µg older dose ranging cohorts.

Program: Tbase_Demo_3_1_PSUR.sas Staburo GmbH. Based on unclean SDTM data received on 21JUN2021 with cutoff 18JUN2021.

Appendix 2.3C Cumulative Summary Tabulations of Demographic Data (Fosun BNT162-03 and BNT162-06)
BNT162/PF-07302048

	BNT162b1 10µg (N=48)	BNT162b1 30µg (N=48)	Placebo (N=48)	BNT162b2/ Placebo (959)	TOTAL* (N = 1103)
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 (100.0)	48 (100.0)	48 (100.0)	959 (100.0)	1103 (100.0)
Other	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Chinese Nationality					
Han Nationality n (%)	48 (100.0)	48 (100.0)	48 (100.0)	959 (100.0)	1103 (100.0)
Other n (%)	30 (100)	118 (98)	245 (100)	46 (96)	47 (98)
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 (41.0%)
*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 cutoff 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-JUN-2021

	B7471026: Blinded Therapy (N=557)	Total (N=557)
Age (years)		
<=17	0	0
18-30	0	0
31-50	0	0
51-64	0	0
65-74	418 (75.0)	418 (75.0)
>=75	139 (25.0)	139 (25.0)
UNSPECIFIED	0	0
Mean	71.50	71.50
Median (range)	71.00 (65- 86)	71.00 (65- 86)
Race, n (%)		
WHITE	500 (89.8)	500 (89.8)
BLACK	23 (4.1)	23 (4.1)
ASIAN	26 (4.7)	26 (4.7)
HISPANIC	3 (0.5)	3 (0.5)
OTHER	5 (0.9)	5 (0.9)
UNSPECIFIED	0	0
Gender, n (%)		
MALE	317 (56.9)	317 (56.9)
FEMALE	240 (43.1)	240 (43.1)