PREPARED BY PFIZER INC

CDS EFFECTIVE DATE: 10-MAY-2022

Date of Superseded CDS: 23-Mar-2022

COVID-19 mRNA Vaccine

CORE DATA SHEET

VERSION 13

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1. NAME OF THE MEDICINAL PRODUCT

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

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

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

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

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

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

For the full list of excipients, see Section 6.1.

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

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

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

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

For the full list of excipients, see Section 6.1.

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

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

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

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

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM[2,3,72]

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

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

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

TRADENAME (Do Not Dilute): Dispersion for injection.

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

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

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

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

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

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

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4.2. Posology and method of administration

Posology

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

Individuals 12 years of age and older

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

Booster dose in individuals 16 years of age and older

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

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

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

Interchangeability

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

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

For further information on efficacy, see Section 5.1.

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

Individuals 5 through <12 years of age

TRADENAME (for age 5 years to <12 years) is administered intramuscularly after dilution as a primary series of 2 doses (0.2 mL) at greater than or equal to 21 days (preferably 3 weeks) apart.[73]

Booster dose in individuals 5 through <12 years of age

A booster dose of TRADENAME (for age 5 years to <12 years of age) may be administered intramuscularly at least 6 months after the second dose in individuals 5 years through <12 years of age.[84]

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

Interchangeability

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

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

For further information on efficacy, see Section 5.1.

Pediatric population

The safety and efficacy of TRADENAME in individuals under 5 years of age have not yet been established. The safety and effectiveness of a booster dose of TRADENAME in individuals 16 through 17 years of age is based on safety and effectiveness data in adults at least 18 through 55 years of age.[71]

Geriatric population

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

The safety of a booster dose of TRADENAME in individuals 65 years of age and older is based on safety data in 12 booster dose recipients 65 through 85 years of age in Study 2, 306 booster dose recipients 18 through 55 years of age in Study 2, and 1,175 booster dose recipients 65 years of age and older in Study 4. The effectiveness of a booster dose of TRADENAME in individuals

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65 years of age and older is based on effectiveness data in 306 booster dose recipients 18 through 55 years of age in Study 2, and an efficacy analysis from participants 16 years of age and older in 9,945 participants in Study 4.[71, 80]

Method of administration

Administer TRADENAME intramuscularly in the deltoid muscle.

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

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

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

Individuals 12 years of age and older

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

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

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

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

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

Individuals 12 years of age and older

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

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

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

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

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

Individuals 5 through <12 years of age

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

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

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

4.3. Contraindications

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

4.4. Special warnings and precautions for use

Traceability

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

General recommendations

As with all injectable vaccines, appropriate medical treatment and supervision must always be readily available in case of a rare anaphylactic event following the administration of the vaccine.[9]

Very rare cases of myocarditis and pericarditis have been reported following vaccination with TRADENAME. Typically, the cases have occurred more often in younger men and after the second dose of the vaccine and within 14 days after vaccination. These are generally mild cases and individuals tend to recover within a short time following standard treatment and rest. Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis in vaccine recipients.[69]

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

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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.

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4.8. Undesirable effects

Summary of safety profile

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

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

In Study C4591031 (Study 4), a placebo-controlled booster study, 5,081 participants 16 years of age and older were recruited from Study 2 to receive a booster dose of TRADENAME at least 6 months after the second dose. The overall safety profile for the booster dose was similar to that seen after 2 doses.80

In a subset of Study 3 Phase 2/3 participants, 401 participants 5 through <12 years of age received a booster dose of TRADENAME at least 5 months after completing the primary series. The overall safety profile for the booster dose was similar to that seen after the primary series.[84]

Participants 16 years of age and older – after 2 doses

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

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

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

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

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Adolescents 12 through 15 years of age – after 2 doses[81]

In an analysis of long-term safety follow-up in Study 2, 2,260 adolescents (1,131 TRADENAME; 1,129 placebo) were 12 through 15 years of age. Of these, 1,559 adolescents (786 TRADENAME and 773 placebo) have been followed for ≥4 months after the second dose.[41,42] The safety evaluation in Study 2 is ongoing.

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

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

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

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

Participants 16 years of age and older – after booster dose[71]

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

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

In Study 4, a placebo-controlled booster study, participants 16 years of age and older recruited from Study 2 received a booster dose of TRADENAME (5,081 participants), or placebo (5,044 participants) at least 6 months after the second dose of TRADENAME. Overall, participants who received a booster dose, had a median follow-up time of 2.5 months after the booster dose to the cut-off date (5 October 2021).[80]

Children 5 through <12 years of age – after booster dose[84]

In a subset from Study 3, a total of 401 children 5 through <12 years of age received a booster dose of TRADENAME 10 mcg at least 5 months (range of 5 to 9 months) after completing the primary series. The analysis of the Study 3 Phase 2/3 subset is based on data up to the cut-off date of March 22, 2022 (median follow-up time of 1.3 months).

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The most frequent adverse reactions in participants 5 through <12 years of age were injection site pain (>70%), fatigue (>40%), headache (>30%), myalgia, chills, injection site redness, and swelling (>10%).

Table 1. Adverse Drug Reactions[13,14,16,64,80]

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

a. A higher frequency of lymphadenopathy was observed in participants 5 through <12 years of age in Study 3 (2.5% vs. 0.9%) and in participants 16 years of age and older in Study 4 (2.8% vs. 0.4%) receiving a booster dose compared to participants receiving 2 doses.[71,84]
b. A higher frequency of pyrexia was observed after the second dose compared to the first dose. The preferred term pyrexia is a cluster term covering also body temperature increased.

Adverse reactions from TRADENAME post-authorization experience

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

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Table 2. Adverse Drug Reactions[38,64,80]

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)[a]

a. A higher frequency of pain in extremity (1.1% vs. 0.8%) was observed in participants receiving a booster dose in Study 4 compared to participants receiving 2 doses.

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

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worsening disease during the 6 weeks before enrollment,[21] were included as were participants with known stable infection with HIV, hepatitis C virus (HCV), or hepatitis B virus (HBV).[12]

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

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

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

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

	TRADENAME (N=18,242) n (%)	**Placebo (N=18,379) n (%)**
Sex		
Male	9318 (51.1)	9225 (50.2)
Female	8924 (48.9)	9154 (49.8)
Age (years)		
Mean (SD)	50.6 (15.70)	50.4 (15.81)
Median	52.0	52.0
Min, max	(12, 89)	(12, 91)
Age group		
12 to 15 years	46 (0.3)	42 (0.2)
16 to 17 years	66 (0.4)	68 (0.4)
16 to 64 years	14,216 (77.9)	14,299 (77.8)
65 to 74 years	3176 (17.4)	3226 (17.6)
≥75 years	804 (4.4)	812 (4.4)
Race		
White	15,110 (82.8)	15,301 (83.3)
Black or African American	1617 (8.9)	1617 (8.8)
American Indian or Alaska Native	118 (0.6)	106 (0.6)
Asian	815 (4.5)	810 (4.4)
Native Hawaiian or other Pacific Islander	48 (0.3)	29 (0.2)
Other[b]	534 (2.9)	516 (2.8)

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	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)

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.

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Table 4. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Age Subgroup – Participants Without Evidence of Infection and Participants With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

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

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting).
Abbreviations: NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.

* Participants who had no evidence of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

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

b. n1 = Number of participants meeting the endpoint definition.

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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 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. 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]

	TRADENAME N[a]=18,198	Placebo N[a]=18,325	
Subgroup	Cases n1[b] Surveillance Time[c] (n2[d])	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.

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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)

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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.

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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)
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)

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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 1,000 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)

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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]
Country			
Argentina	16 1.033 (2655)	110 1.017 (2670)	85.7 (75.7, 92.1)
Brazil	14 0.441 (1419)	82 0.408 (1401)	84.2 (71.9, 91.7)
Germany	0 0.047 (237)	1 0.048 (243)	100.0 (-3868.6, 100.0)
South Africa	0 0.099 (358)	10 0.096 (358)	100.0 (56.6, 100.0)
Turkey	0 0.029 (238)	6 0.026 (232)	100.0 (22.2, 100.0)
United States	51 4.861 (16,735)	664 4.678 (16,785)	92.6 (90.2, 94.6)

Notes: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting). Included confirmed cases in participants 12 through 15 years of age: 0 in the TRADENAME group; 18 in the placebo group.

* Participants who had no evidence of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

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.

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Table 9. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – Participants Without Evidence of Infection* Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population[23]

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

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c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
f. At risk is defined as having at least 1 of the Charlson Comorbidity Index (CMI) category or obesity (BMI ≥30 kg/m^2).
g. Obese is defined as BMI ≥30 kg/m^2.

The updated subgroup analyses of vaccine efficacy by risk status in participants followed up to 6 months after Dose 2 (with a cut-off date of 13 March 2021) are presented in Table 10 and Table 11.

Table 10. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – Participants Without Evidence of Infection* Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period[55]

Subgroup	TRADENAME N[a]=20,998 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=21,096 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]
First COVID-19 occurrence from 7 days after Dose 2[f]	77 6.247 (20,712)	850 6.003 (20,713)	91.3 (89.0, 93.2)
At risk[g]			
Yes	35 2.797 (9167)	401 2.681 (9136)	91.6 (88.2, 94.3)
No	42 3.450 (11,545)	449 3.322 (11,577)	91.0 (87.6, 93.6)
Age group (years) and risk status			
16 through 64 and not at risk	41 2.776 (8887)	385 2.661 (8886)	89.8 (85.9, 92.8)
16 through 64 and at risk	29 2.083 (6632)	325 1.993 (6629)	91.5 (87.5, 94.4)
65 and older and not at risk	1 0.553 (1870)	53 0.546 (1922)	98.1 (89.2, 100.0)
65 and older and at risk	6 0.680 (2322)	71 0.656 (2304)	91.8 (81.4, 97.1)
Obese[h]			
Yes	27 2.103 (6796)	314 2.050 (6875)	91.6 (87.6, 94.6)
No	50 4.143 (13,911)	536 3.952 (13,833)	91.1 (88.1, 93.5)

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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]
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.

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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)

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.

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

Efficacy against severe COVID-19 - after 2 doses

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

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

As of 13 March 2021, vaccine efficacy against severe COVID-19 is presented only for participants with or without prior SARS-CoV-2 infection (Table 12) as the COVID-19 case counts in participants without prior SARS-CoV-2 infection were the same as those in participants with or without prior SARS-CoV-2 infection in both the TRADENAME and placebo groups.

Table 12. Vaccine Efficacy – First Severe COVID-19 Occurrence in Participants With or Without* Prior SARS-CoV-2 Infection Based on FDA† or Centers for Disease Control and Prevention (CDC)‡ Definition After Dose 1 or From 7 Days After Dose 2 in the Placebo-Controlled Follow-up

Vaccine Efficacy – First Severe COVID-19 Occurrence Based on FDA Definition[57,58]			
	TRADENAME Cases n1[a] Surveillance Time (n2[b])	**Placebo Cases n1[a] Surveillance Time (n2[b])**	**Vaccine Efficacy % (95% CI[c])**
After Dose 1[d]	1 8.439[e] (22,505)	30 8.288[e] (22,435)	96.7 (80.3, 99.9)
7 days after Dose 2[f]	1 6.522[g] (21,649)	21 6.404[g] (21,730)	95.3 (70.9, 99.9)

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

Efficacy and immunogenicity in adolescents 12 to 15 years of age – after 2 doses

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

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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 through 25 years of age who had no serological or virological evidence of past SARS-CoV-2 infection. The immune response to TRADENAME in adolescents 12 to 15 years of age (n=190) was non-inferior to the immune

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response in participants 16 through 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 through 25 years of age group was 1.76, with a 2-sided 95% CI of 1.47 to 2.10, meeting the 1.5-fold non-inferiority criterion (the lower bound of the 2-sided 95% CI for the 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 through 25 years of age.[48]

An updated efficacy analysis of Study 2 has been performed in approximately 2,260 adolescents 12 through 15 years of age evaluating confirmed COVID-19 cases accrued up to a data cut-off date of September 2, 2021, representing up to 6 months of follow-up after Dose 2 for participants in the efficacy population.[81]

The updated vaccine efficacy information in adolescents 12 through 15 years of age is presented in Table 14.

Table 14: 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 Through 15 Years of Age Evaluable Efficacy (7 Days) Population[81]

First COVID-19 occurrence from 7 days after Dose 2 in adolescents 12 through 15 years of age without evidence of prior SARS-CoV-2 infection*			
	TRADENAME N[a]=1057 Cases n1[b] Surveillance Time[c] (n2[d])	**Placebo N[a]=1030 Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI[e])**
Adolescents 12 through 15 years of age	0 0.343 (1043)	28 0.322 (1019)	100.0 (86.8, 100.0)
First COVID-19 occurrence from 7 days after Dose 2 in adolescents 12 through 15 years of age with or without evidence of prior SARS-CoV-2 infection			
	TRADENAME N[a]=1119 Cases n1[b] Surveillance Time[c] (n2[d])	**Placebo N[a]=1109 Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI[e])**
Adolescents 12 through 15 years of age	0 0.362 (1098)	30 0.345 (1088)	100.0 (87.5, 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).

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* 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.

Efficacy in children 5 through <12 years of age – after 2 doses

A descriptive efficacy analysis of Study 3 has been performed in 1,968 children 5 through <12 years of age without evidence of infection prior to 7 days after Dose 2. This analysis evaluated confirmed symptomatic COVID-19 cases accrued up to a data cut-off date of October 8, 2021.[82]

Table 15 presents the specific demographic characteristics in participants who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose.

Table 15: Demographics Characteristics – Participants Without Evidence of Infection Prior to 7 Days After Dose 2 – Phase 2/3 – 5 Through <12 Years of Age – Evaluable Efficacy Population[82]

	TRADENAME* 10 mcg/dose (N^a=1305) n^b (%)	**Placebo (N^a=663) n^b (%)**
Sex		
Male	679 (52.0)	343 (51.7)
Female	626 (48.0)	320 (48.3)
Age at Vaccination		
Mean (SD)	8.2 (1.93)	8.1 (1.98)
Median	8.0	8.0
Min, max	(5, 11)	(5, 11)

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	TRADENAME* 10 mcg/dose (N[a]=1305) n[b] (%)	**Placebo (N[a]=663) n[b] (%)**
Race		
White	1018 (78.0)	514 (77.5)
Black or African American	76 (5.8)	48 (7.2)
American Indian or Alaska Native	<1.0%	<1.0%
Asian	86 (6.6)	46 (6.9)
Native Hawaiian or other Pacific Islander	<1.0%	<1.0%
Other[c]	110 (8.4)	52 (7.8)
Ethnicity		
Hispanic or Latino	243 (18.6)	130 (19.6)
Not Hispanic or Latino	1059 (81.1)	533 (80.4)
Not reported	<1.0%	<1.0%
Comorbidities[d]		
Yes	262 (20.1)	133 (20.1)
No	1043 (79.9)	530 (79.9)

* Pfizer-BioNTech COVID-19 Vaccine (10 mcg modRNA).

a. N = number of participants in the specified group from the evaluable efficacy population with no evidence of SARS CoV-2 infection prior to 7 days after Dose 2. This value is the denominator for the percentage calculations. Evaluable efficacy population included all eligible randomized participants who received all vaccination(s) as randomized within the predefined window, had no other important protocol deviations as determined by the clinician.

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

c. Includes multiracial and not reported.

d. Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as participants who had at least 1 of the prespecified comorbidities based on MMWR 69(32);1081-1088 and/or obesity (BMI ≥95th percentile).

The descriptive vaccine efficacy results in children 5 through <12 years of age without evidence of prior SARS-CoV-2 infection are presented in Table 16. None of the cases accrued met criteria for severe COVID-19 or multisystem inflammatory syndrome in children (MIS-C). No cases of COVID-19 were observed in either the vaccine group or the placebo group in participants with evidence of prior SARS-CoV-2 infection.[82]

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Table 16: Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2: Without Evidence of Infection Prior to 7 Days After Dose 2 – Phase 2/3 – Children 5 Through <12 Years of Age Evaluable Efficacy Population[82]

First COVID-19 occurrence from 7 days after Dose 2 in children 5 through <12 years of age without evidence of prior SARS-CoV-2 infection*			
	TRADENAME± 10 mcg/dose N[a]=1305 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=663 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)
Children 5 through 11 years of age	3 0.322 (1273)	16 0.159 (637)	90.7 (67.7, 98.3)

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

* Participants who had no evidence of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

± Pfizer-BioNTech COVID-19 Vaccine (10 mcg modRNA).

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

b. n1 = Number of participants meeting the endpoint definition.

c. Total surveillance time in 1,000 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.

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

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

In Study 3, an analysis of SARS-CoV-2 50% neutralizing titers (NT50) 1 month after Dose 2 in a randomly selected subset of participants demonstrated effectiveness by immunobridging of immune responses comparing children 5 through <12 years of age in the Phase 2/3 part of Study 3 to participants 16 through 25 years of age in the Phase 2/3 part of Study 2 who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2, meeting the prespecified immunobridging criteria for both the GMR and the seroresponse difference with seroresponse defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from baseline (before Dose 1).

The ratio of the SARS-CoV-2 NT50 in children 5 through <12 years of age to that of young adults 16 through 25 years of age was 1.04 (2-sided 95% CI: 0.93, 1.18), as presented in Table 17.

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Table 17: Summary of Geometric Mean Ratio for 50% Neutralizing Titer – Comparison of Children 5 Through <12 Years of Age (Study 3) to Participants 16 Through 25 Years of Age (Study 2) – Participants Without* Evidence of Infection up to 1 Month After Dose 2 – Dose 2 Evaluable Immunogenicity Population[73]

		TRADENAME			
		10 mcg/Dose 5 Through <12 Years n[a]=264	30 mcg/Dose 16 Through 25 Years n[a]=253	5 Through <12 Years/ 16 Through 25 Years	
Assay	Time Point[b]	GMT[c] (95% CI[c])	GMT[c] (95% CI[c])	GMR[d] (95% CI[d])	Met Immunobridging Objective[e] (Y/N)
SARS-CoV-2 neutralization assay - NT50 (titer)[f]	1 month after Dose 2	1197.6 (1106.1, 1296.6)	1146.5 (1045.5, 1257.2)	1.04 (0.93, 1.18)	Y

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

* Participants who had no serological or virological evidence (up to 1 month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and 1 month after Dose 2, SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT (nasal swab) at any unscheduled visit up to 1 month after Dose 2 blood collection) and had no medical history of COVID-19 were included in the analysis.

a. n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.

b. Protocol-specified timing for blood sample collection.

c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.

d. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titers (Group 1[5 through <12 years of age] - Group 2 [16 through 25 years of age]) and the corresponding CI (based on the Student t distribution).

e. Immunobridging is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥0.8.

f. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, 99.2% of children 5 through <12 years of age and 99.2% of participants 16 through 25 years of age had a seroresponse from before vaccination to 1 month after Dose 2. The difference in proportions of participants who had seroresponse between the 2 age groups (children – young adult) was 0.0% (2-sided 95% CI: -2.0%, 2.2%), as presented in Table 18.

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Table 18: Difference in Percentages of Participants With Seroresponse – Participants Without* Evidence of Infection up to 1 Month After Dose 2 – Immunobridging Subset – Phase 2/3 – Comparison of 5 Through <12 Years of Age to Study 2 Phase 2/3 16 Through 25 Years of Age – Evaluable Immunogenicity Population[73]

		Pfizer-BioNTech COVID-19 Vaccine			
		Study 3 10 mcg/Dose 5 Through <12 Years N[a]=264	Study 2 30 mcg/Dose 16 Through 25 Years N[a]=253	5 Through <12 Years / 16 Through 25 Years	
Assay	Time Point[b]	n[c] (%) (95% CI[d])	n[c] (%) (95% CI[d])	Difference %[e] (95% CI[f])	Met Immunobridging Objective[g] (Y/N)
SARS-CoV-2 neutralization assay - NT50 (titer)[h]	1 month after Dose 2	262 (99.2) (97.3, 99.9)	251 (99.2) (97.2, 99.9)	0.0 (-2.0, 2.2)	Y

Abbreviations: LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer 50; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result ≥4 × LLOQ is considered a seroresponse.

* Participants who had no serological or virological evidence (up to 1 month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and 1 month after Dose 2, SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT (nasal swab) at any unscheduled visit up to 1 month after Dose 2 blood collection) and had no medical history of COVID-19 were included in the analysis.

a. N = number of participants with valid and determinate assay results both before vaccination and at 1 month after Dose 2. These values are the denominators for the percentage calculations.
b. Protocol-specified timing for blood sample collection.
c. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.
d. Exact 2-sided CI based on the Clopper and Pearson method.
e. Difference in proportions, expressed as a percentage (Group 1 [5 through <12 years of age] – Group 2 [16 through 25 years of age]).
f. 2-Sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
g. Immunobridging is declared if the lower bound of the 2-sided 95% CI for the difference in proportions is greater than -10.0%.
h. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

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

Effectiveness of a booster dose of TRADENAME was demonstrated by evaluating noninferiority immune responses of SARS-CoV-2 NT50 1 month after a booster dose. In Study 2, an analysis of SARS-CoV-2 NT50 demonstrated non-inferior immune responses 1 month after a booster dose

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compared to 1 month after Dose 2 in participants at least 18 through 55 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the booster dose, based on prespecified noninferiority criteria for both GMR and difference in seroresponse rates. Seroresponse for a participant was defined as achieving a ≥4-fold rise from baseline (before Dose 1) in NT50 (Table 19 and Table 20).

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

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

Table 19: Summary of Geometric Mean Ratio for 50% Neutralizing Titer – Comparison of 1 Month After Booster Dose to 1 Month After Dose 2 – Participants Without Evidence of Infection up to 1 Month After Booster Dose* – Booster Dose Evaluable Immunogenicity Population[71]

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

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

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

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

b. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.

c. GMRs and 2-sided 97.5% CIs were calculated by exponentiating the mean differences in the logarithms of the assay and the corresponding CIs (based on the Student t distribution).

d. Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the GMR is >0.67 and the point estimate of the GMR is ≥0.80.

e. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on

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Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

Table 20: Percentage Difference of Participants Achieving Seroresponse – Comparison of 1 Month After Booster Dose to 1 Month After Dose 2 – Phase 3 – Participants Without Evidence of Infection up to 1 Month After Booster Dose* – Booster Dose Evaluable Immunogenicity Population[71]

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

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

Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result ≥4 × LLOQ is considered a seroresponse.

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

a. N = number of participants with valid and determinate assay results for the specified assay at baseline, 1 month after Dose 2 and 1 month after the booster dose within specified window. These values are the denominators for the percentage calculations.

b. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.

c. Exact 2-sided CI based on the Clopper and Pearson method.

d. Difference in proportions, expressed as a percentage (1 month after booster dose – 1 month after Dose 2).

e. Adjusted Wald 2-sided CI for the difference in proportions, expressed as a percentage.

f. Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the percentage difference is >-10%.

g. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

Relative vaccine efficacy in participants 16 years of age and older – after booster dose[80]

An interim efficacy analysis of Study 4, a placebo-controlled booster study, was performed in approximately 10,000 participants 16 years of age and older who were recruited from Study 2, evaluated confirmed COVID-19 cases accrued from at least 7 days after booster vaccination up to a data cut-off date of 5 October 2021, which represents a median of 2.5 months post-booster follow-up. Vaccine efficacy of the TRADENAME booster dose after the primary series relative to the placebo booster group who only received the primary series dose was assessed. The relative vaccine efficacy information for participants 16 years of age and older is presented in Table 21.

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Table 21: Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Booster Vaccination – Participants 16 Years of Age and Older Without Evidence of Infection and Participants With or Without Evidence of Infection Prior to 7 Days After Booster Vaccination – Evaluable Efficacy Population[80]

First COVID-19 occurrence from 7 days after booster dose in participants without evidence of prior SARS-CoV-2 infection*			
	Comirnaty Na=4695 Cases n1b Surveillance Timec (n2d)	**Placebo Na=4671 Cases n1b Surveillance Timec (n2d)**	**Relative Vaccine Efficacye % (95% CIf)**
First COVID-19 occurrence from 7 days after booster vaccination	6 0.823 (4659)	123 0.792 (4614)	95.3 (89.5, 98.3)
First COVID-19 occurrence from 7 days after booster dose in participants with or without evidence of prior SARS-CoV-2 infection			
	Comirnaty Na=4993 Cases n1b Surveillance Timec (n2d)	**Placebo Na=4952 Cases n1b Surveillance Timec (n2d)**	**Relative Vaccine Efficacye % (95% CIf)**
First COVID-19 occurrence from 7 days after booster vaccination	7 0.871 (4934)	124 0.835 (4863)	94.6 (88.5, 97.9)

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 serological or virological evidence (prior to 7 days after receipt of the booster vaccination) 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 Visit 1, and had a negative NAAT [nasal swab] at any unscheduled visit prior to 7 days after booster vaccination) 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 the booster vaccination to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Relative vaccine efficacy of the Comirnaty booster group relative to the placebo group (non-booster).
f. Two-sided confidence interval (CI) for relative vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.

Immunogenicity in children 5 through <12 years of age – after booster dose[84]

Effectiveness of a booster dose of TRADENAME was based on an assessment of NT50 against the reference strain of SARS-CoV-2 (USA_WA1/2020). Analyses of NT50 1 month after the booster dose compared to before the booster dose (Dose 3) demonstrated a substantial increase in

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GMTs in individuals 5 through <12 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the booster dose. This analysis is summarized in Table 22.

Table 22: Summary of Geometric Mean Titers – NT50 – Participants Without Evidence of Infection – Phase 2/3 – Immunogenicity Set – 5 Through <12 Years of Age – Evaluable Immunogenicity Population

		Pfizer-BioNTech COVID-19 Vaccine 10 mcg/Dose					
		3-Dose Set		2-Dose Set		Total	
Assay	Dose/ Sampling Time Point[a]	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])
SARS-CoV-2 neutralization assay - NT50 (titer)	1 month Prevax	79	20.5 (20.5, 20.5)	67	20.5 (20.5, 20.5)	146	20.5 (20.5, 20.5)
	1 month after Dose 2	29	1659.4 (1385.1, 1988.0)	67	1110.7 (965.3, 1278.1)	96	1253.9 (1116.0, 1408.9)
	3 months Prevax	67	271.0 (229.1, 320.6)	-	-	67	271.0 (229.1, 320.6)
	1 month after Dose 3	67	2720.9 (2280.1, 3247.0)	-	-	67	2720.9 (2280.1, 3247.0)

Abbreviations: CI = confidence interval; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer; Prevax = before vaccination; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Three-dose immunogenicity set included the first 130 participants who received Dose 3 and completed 1-month post–Dose 3 visit prior to March 15, 2022. Among those, 30 had blood sample collection at 1-month post-Dose 2. Two-dose immunogenicity set included an extra 67 participants randomly selected from previous Dose-2 evaluable immunogenicity population and without evidence of infection up to 1-month post–Dose 2 subset used for 2-dose immunobridging analysis.
Note: Participants included in this analysis had no serological or virological evidence of past SARS-CoV-2 infection up to the 1-month post–Dose 2 (for 1-month post–Dose 2 time point) or 1-month post–Dose 3 (for pre–Dose 3 and 1-month post–Dose 3 time point) study blood sample collection. Having no evidence of past SARS-CoV-2 infection up to 1-month post–Dose 2 was defined as having a negative N-binding antibody (serum) result at the Dose 1 and 1-month post–Dose 2 study visits; a negative NAAT (nasal swab) result at the Dose 1 and Dose 2 study visits and any unscheduled visit prior to the 1-month post–Dose 2 blood sample collection; and no medical history of COVID-19. Having no evidence of past SARS-CoV-2 infection up to 1-month post-Dose 3 was defined as having a negative N-binding antibody (serum) result at the Dose 1, 1-month post–Dose 2 (if available), Dose 3, and 1-month post–Dose 3 study visits; a negative NAAT (nasal swab) result at the Dose 1, Dose 2, and Dose 3 study visits and any unscheduled visit prior to the 1-month post–Dose 3 blood sample collection; and no medical history of COVID-19.

a. Protocol-specified timing for blood sample collection.
b. n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.

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Immunogenicity in children 5 through <12 years of age on the Omicron variant – after booster dose[84]

The neutralizing GMTs against both the Omicron variant and reference strain were substantially increased after booster vaccination compared with after the 2-dose primary series. At 1-month post-Dose 2, the observed neutralizing GMTs for the Omicron variant and reference strain were 27.6 and 323.8, respectively. At 1-month post-Dose 3, the observed neutralizing GMTs for the Omicron variant and reference strain were 614.4 and 1702.8, respectively (see Table 23).

For the Omicron variant, neutralizing titers after booster vaccination (1-month post-Dose 3) increased 22-fold over those after the 2-dose primary series (1-month post-Dose 2). For the reference strain, the increase after the booster relative to the primary series was 5.3-fold.

Table 23: Summary of Geometric Mean Titers – Omicron-Neutralization Subset – Participants Without Evidence of Infection – Phase 2/3 – Immunogenicity Set – 5 Through <12 Years of Age – Evaluable Immunogenicity Population

		Pfizer-BioNTech COVID 19 Vaccine 10 mcg/Dose	
		Vaccine Group (as Randomized)	
Assay	Time Point[b]	n[b]	GMT[c] (95% CI[c])
SARS-COV-2 FFRNT- B.1.1.529 strain (Omicron) - NT50 (titer)	1 month after Dose 2	29	27.6 (22.1, 34.5)
	1 month after Dose 3	17	614.4 (410.7, 919.2)
SARS-CoV-2 FFRNT- reference strain - NT50 (titer)	1 month after Dose 2	29	323.8 (267.5, 392.1)
	1 month after Dose 3	17	1702.8 (1282.6, 2260.7)

Abbreviations: CI = confidence interval; FFRNT = fluorescence focus reduction neutralization test; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Participants included in this analysis had no serological or virological evidence of past SARS-CoV-2 infection up to the 1-month post–Dose 2 (for 1-month post–Dose 2 time point) or 1-month post–Dose 3 (for 1-month post–Dose 3 time point) study blood sample collection. Having no evidence of past SARS-CoV-2 infection up to 1-month post–Dose 2 was defined as having a negative N-binding antibody (serum) result at the Dose 1 and 1-month post–Dose 2 study visits; a negative NAAT (nasal swab) result at the Dose 1 and Dose 2 study visits and any unscheduled visit prior to the 1-month post–Dose 2 blood sample collection; and no medical history of COVID-19. Having no evidence of past SARS-CoV-2 infection up to 1-month post–Dose 3 was defined as having a negative N-binding antibody (serum) result at the Dose 1, 1-month post–Dose 2 (if available), Dose 3, and 1-month post–Dose 3 study visits; a negative NAAT (nasal swab) result at the Dose 1, Dose 2, and Dose 3 study visits and any unscheduled visit prior to the 1-month post–Dose 3 blood sample collection; and no medical history of COVID-19.

a. Protocol-specified timing for blood sample collection.
b. n = Number of participants with valid and determinate assay results for the specified assays at the given dose/sampling time point.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.

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5.2. Pharmacokinetic properties

Not applicable.

5.3. Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

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

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

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

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

TRADENAME (Do Not Dilute)

Or

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

TRADENAME (for age 5 years to <12 years)

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

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Tromethamine
Tromethamine hydrochloride
Sucrose
Water for injections

6.2. Incompatibilities

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

6.3. Shelf life

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

TRADENAME (Dilute Before Use)

Unopened vial

12 months at -90 °C to -60 °C.[63,70,83]

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 ºC to -60 ºC; not exceeding the printed expiry date (EXP).[39]

Once removed from the freezer, the unopened vial can be stored for up to 1 month at 2 °C to 8 °C; not exceeding the printed expiry date (EXP). 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.

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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.

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

TRADENAME (Do Not Dilute)[75]

Unopened vial

12 months when stored at -90 °C to -60 °C.[79,83]

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

Once removed from frozen storage, the unopened vial may be stored refrigerated at 2 °C to 8 °C for a single period of up to 10 weeks; not exceeding the printed expiry date (EXP).[79]

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

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

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

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

Thawed vials can be handled in room light conditions.

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

Opened vial

Chemical and physical in-use stability has been demonstrated for 12 hours at 2 ºC to 30 ºC. From a microbiological point of view, unless the method of opening precludes the risks of microbial

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contamination, the product should be used immediately after the first puncture. If not used immediately, in-use storage times and conditions are the responsibility of the user.[77]

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

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

Unopened vial

12 months when stored at -90 °C to -60 °C.[79,83]

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

Once removed from frozen storage, the unopened vial may be stored refrigerated at 2 °C to 8 °C for a single period of up to 10 weeks; not exceeding the printed expiry date (EXP).[79]

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

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

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

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

Thawed vials can be handled in room light conditions.

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

Diluted medicinal product

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

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

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

TRADENAME (Dilute Before Use)

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

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

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

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

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

TRADENAME (Do Not Dilute)

Or

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

TRADENAME (for age 5 years to <12 years)

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

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

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

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

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

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

Once thawed, the vaccine cannot be re-frozen.

Thawed vials can be handled in room light conditions.

6.5. Nature and contents of container

Information to be provided by local subsidiary.

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

Handling instructions

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

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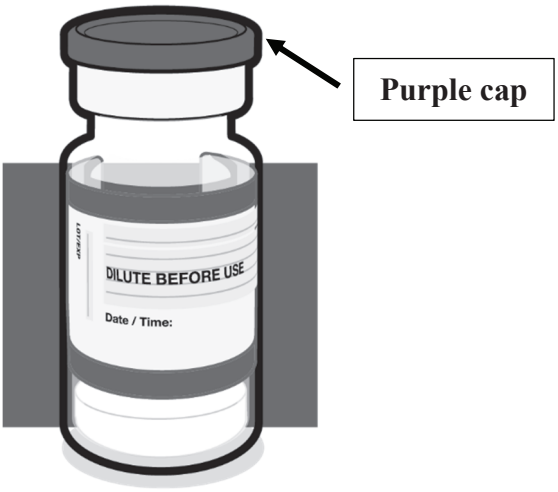
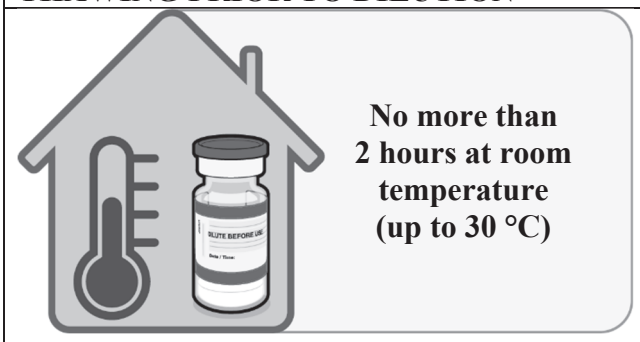
*[Editorial guidance for countries: Select this text for the **PBS/Sucrose presentation, 30 micrograms/dose**.]*

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

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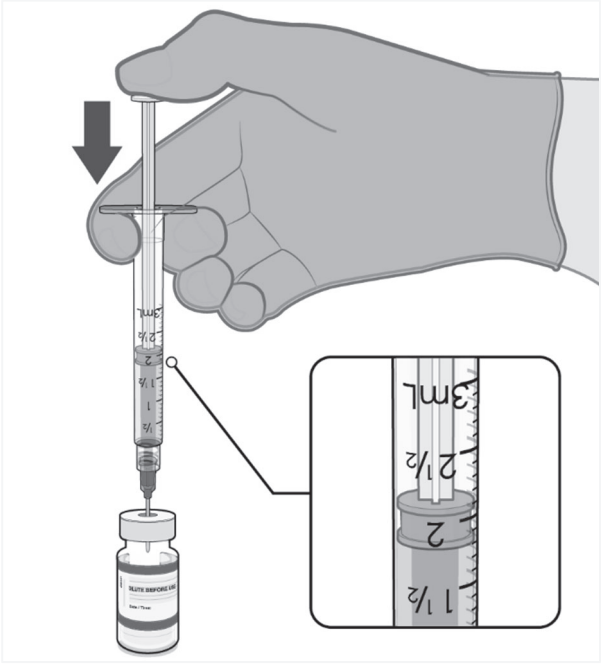
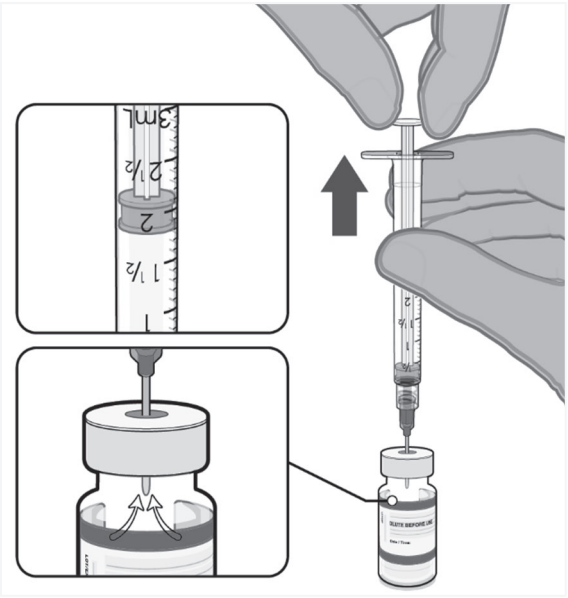
TRADENAME (Dilute Before Use)	
DILUTION	
 **1.8 mL of 0.9% sodium chloride injection**	• The thawed vaccine must be diluted in its original vial with 1.8 mL sodium chloride 9 mg/mL (0.9%) solution for injection, using a 21 gauge or narrower needle and aseptic techniques.
 **Pull back plunger to 1.8 mL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

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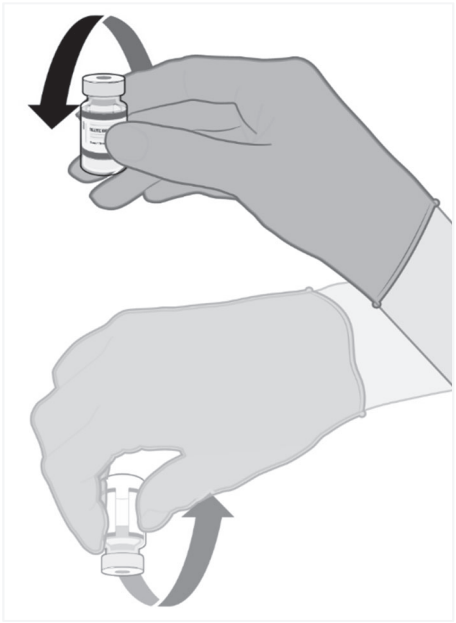
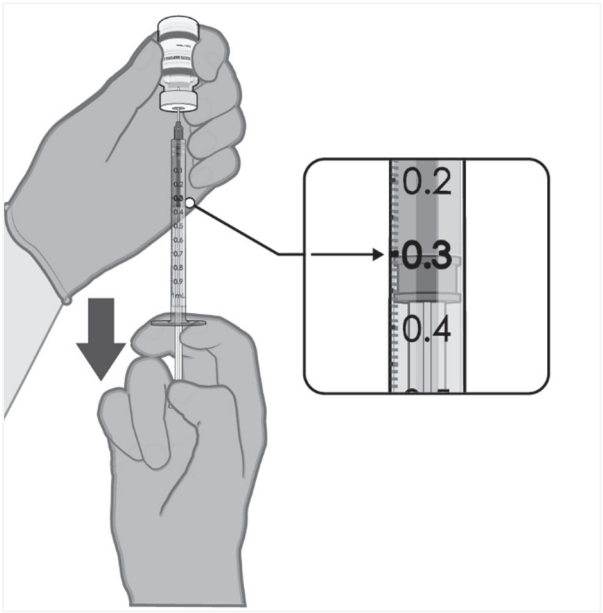
TRADENAME (Dilute Before Use)	
 **Gently × 10**	• Gently invert the diluted dispersion 10 times. Do not shake. • The diluted vaccine should present as an off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discoloration are present.
 **Record appropriate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

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

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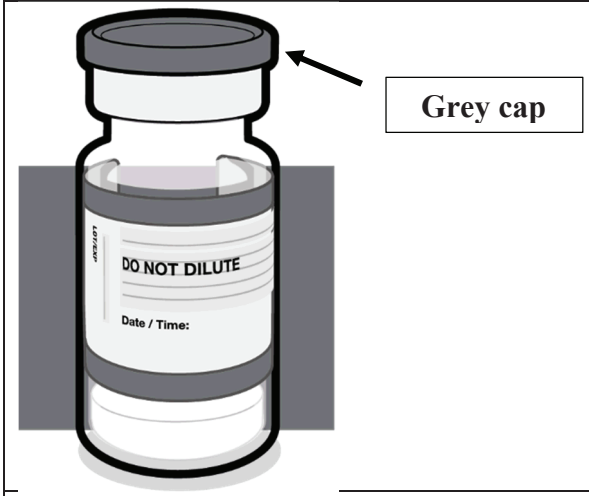
*[Editorial guidance for countries: Select this text for the **Tris/Sucrose presentation, 30 micrograms/dose**.]*

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

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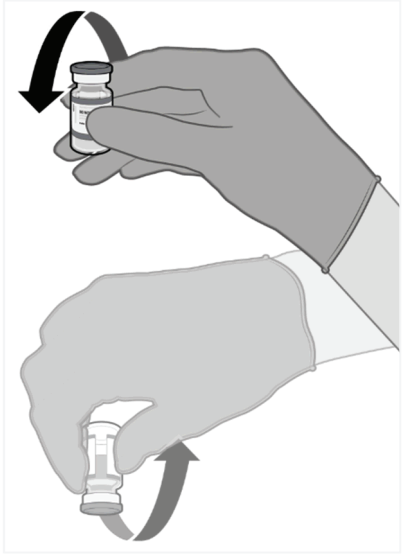
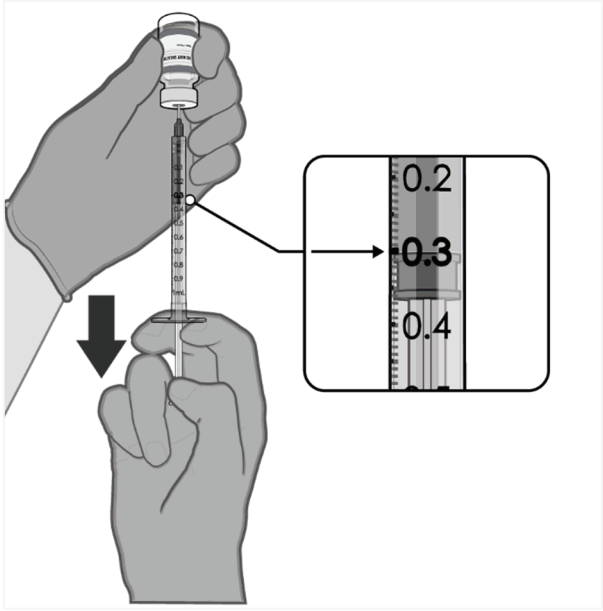
<table>
<tr><th colspan="2">TRADENAME (Do Not Dilute)</th></tr>
<tr><td> 
Gently × 10</td><td>• Gently mix by inverting vials 10 times prior to use. Do not shake.
• Prior to mixing, the thawed dispersion may contain white to off-white opaque amorphous particles.
• After mixing, the vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the vaccine if particulates or discoloration are present.</td></tr>
<tr><th colspan="2">PREPARATION OF INDIVIDUAL 0.3 mL DOSES OF TRADENAME</th></tr>
<tr><td> 

0.3 mL vaccine</td><td>• Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
• Withdraw 0.3 mL of TRADENAME.

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

If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial.
• Each dose must contain 0.3 mL of vaccine.
• If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
• Discard any unused vaccine 12 hours after first puncture. Record the appropriate date/time on the vial.</td></tr>
</table>

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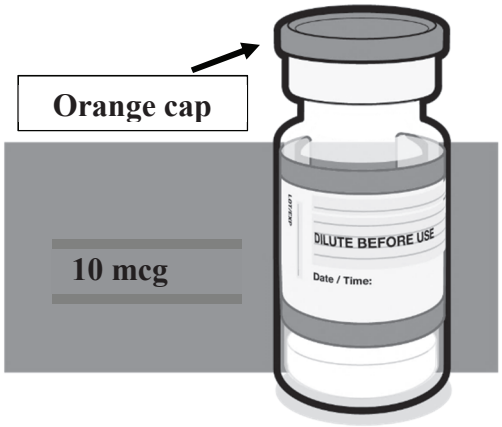
*[Editorial guidance for countries: Select this text for the **Tris/Sucrose presentation, 10 micrograms/dose**.]*

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

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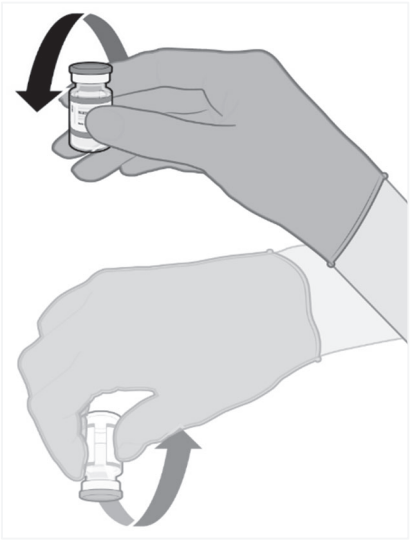
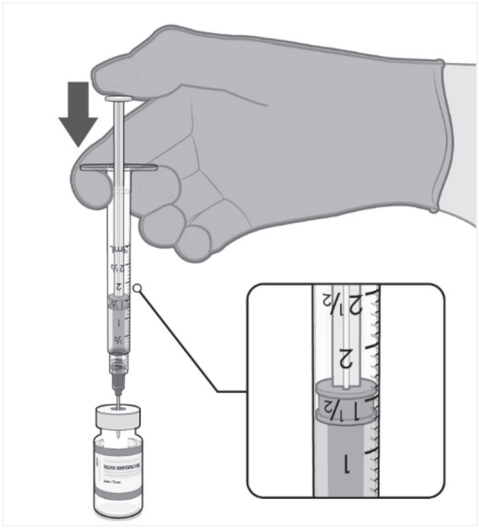
TRADENAME (for age 5 years to <12 years)	
MIXING PRIOR TO DILUTION	
 **Gently × 10**	• Allow the thawed vial to come to room temperature and gently invert it 10 times prior to dilution. Do not shake. • Prior to dilution, the thawed dispersion may contain white to off-white opaque amorphous particles.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

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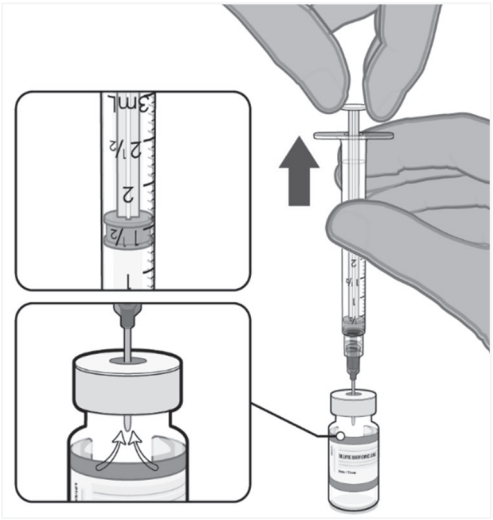
TRADENAME (for age 5 years to <12 years)	
 **Pull back plunger to 1.3 mL to remove air from vial.**	• Equalize vial pressure before removing the needle from the vial stopper by withdrawing 1.3 mL air into the empty diluent syringe.
 **Gently × 10**	• Gently invert the diluted dispersion 10 times. Do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

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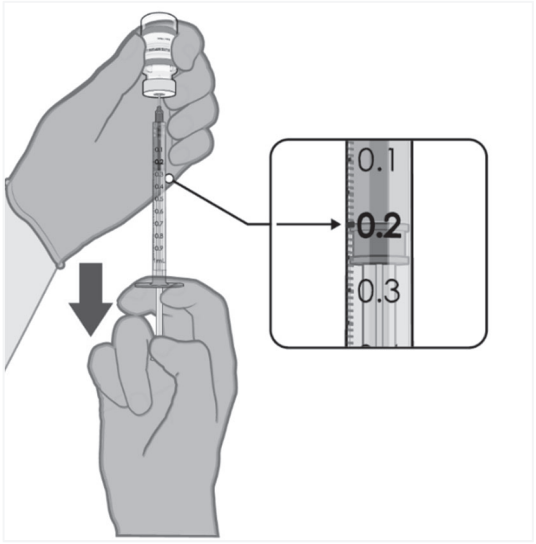
TRADENAME (for age 5 years to <12 years)	
 **Record appropriate date and time.** **Use within 12 hours after dilution.**	• The diluted vials should be marked with the appropriate date and time. • After dilution, store at 2 ºC to 30 ºC and use within 12 hours. • Do not freeze or shake the diluted dispersion.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

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Disposal

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

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7. REFERENCES

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

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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

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41. Module 2.7.4 Summary of Clinical Safety, MAA Type II Variation (12-15 Years) Table 6: Demographic Characteristics – Subjects 12 Through 15 and 16 Through 25 Years of Age – Safety Population
42. Table: Follow-up Time After Dose 2 – Subjects 12 Through 15 Years of Age – Safety Population
43. Table: Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population
44. Table: Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population
45. Table: Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 Through 1 Month After Dose 2, by System Organ Class and Preferred Term – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population
46. Table: Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-up Period – Subjects 12 Through 15 Years of Age and Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
47. Table: Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-up Period – Subjects 12 Through 15 Years of Age and With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
48. Table: Summary of Geometric Mean Ratio – NT50 – Comparison of Subjects 12 Through 15 Years of Age to Subjects 16 Through 25 Years of Age (Immunogenicity Subset) – Subjects Without Evidence of Infection up to 1 Month After Dose 2 – Dose 2 Evaluable Immunogenicity Population
49. Module 2.7.4 Summary of Clinical Safety, COVID-19 Vaccine – MAA Type II Variation (12-15 Years) April 2021
50. Interim Report – 6 Month Update: A Phase 1/2/3, Placebo-Controlled, Randomized, Observer-Blind, Dose-Finding Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of SARS-COV-2 RNA Vaccine Candidates Against COVID-19 in Healthy Individuals [hereafter Interim Report – 6 Month Update] (13 March 2021), Supplemental Table 14.198 Demographic Characteristics, by Age Groups – Phase 2/3 Subjects ≥16 Years of Age – Safety Population
51. Interim Report – 6 Month Update (13 March 2021), Supplemental table 14.84 – Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2 – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 HIV Positive Subjects ≥16 Years of Age – Safety Population
52. Final Analysis Interim Report: A Phase 1/2/3, Placebo-Controlled, Randomized, Observer-Blind, Dose-Finding Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of SARS-COV-2 RNA Vaccine Candidates Against COVID-19 in Healthy

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Individuals (04 November 2020), Section 10.3.3 Phase 2/3, Table 8 Vaccine Administration Timing – ~38000 Subjects for Phase 2/3 Analysis – All Randomized Subjects

53. Interim Report – 6 Month Update (13 March 2021), Table 19. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Subgroup – Blinded Placebo-Controlled Follow-up Period – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
54. Interim Report – 6 Month Update (13 March 2021), Supplemental Table 14.59. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Subgroup– Blinded Placebo-Controlled Follow-up Period–Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
55. Interim Report – 6 Month Update (13 March 2021), Table 20. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – Blinded Placebo-Controlled Follow-up Period – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
56. Interim Report – 6 Month Update (13 March 2021), Table 21. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – Blinded Placebo-Controlled Follow-up Period – Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
57. Interim Report – 6 Month Update (13 March 2021), Table 25. Vaccine Efficacy – First Severe COVID-19 Occurrence From 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-up Period – Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
58. Interim Report – 6 Month Update (13 March 2021), Table 26. Vaccine Efficacy – First Severe COVID-19 Occurrence After Dose 1 – Blinded Placebo-Controlled Follow-up Period – Dose 1 All-Available Efficacy Population
59. Interim Report – 6 Month Update (13 March 2021), Supplemental Table 14.61. Vaccine Efficacy – First Severe COVID-19 Occurrence Based on CDC-Definition After Dose 1 – Blinded Placebo-Controlled Follow-up Period – Dose 1 All-Available Efficacy Population
60. Interim Report – 6 Month Update (13 March 2021), Table 28. Vaccine Efficacy – First Severe COVID-19 Occurrence Based on CDC-Definition From 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-up Period – Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
61. EUA Amendment for Pfizer-BioNTech COVID-19 Vaccine, 6-Month Follow-Up Data from Participants 16 Years of Age and Older (13 March 2021), Section 6.2.1.2.1.2 Efficacy
62. Interim Report – 6 Month Update (13 March 2021), Table 4. Analysis Populations
63. Module 3.2.P.8.1 Stability Summary and Conclusion, August 2021
64. Adverse Drug Reaction Frequency Justification Document, COVID-19 Vaccine (BNT162B2), May 2022
65. Interim Report – 6 Month Update (13 March 2021), Supplemental Table 14.72 – Local Reactions, by Maximum Severity, Within 7 Days After Each Dose (Reactogenicity Subset)

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

66. Interim Report – 6 Month Update (13 March 2021), Supplemental Table 14.79 – Systemic Events, by Maximum Severity, Within 7 Days After Each Dose (Reactogenicity Subset) – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 HIV-Positive Subjects ≥16 Years of Age – Safety Population
67. 2.5 Clinical Overview to Support Inclusion of Vaccine Stress-Related Reactions in Section 4.4 of the Core Data Sheet, May 2021
68. EUA Amendment for Pfizer-BioNTech COVID-19 Vaccine, 6-Month Follow-Up Data from Participants 16 Years of Age and Older (13 March 2021), Section 6.2.2.1.1 Study Populations – BNT162-01 Phase 1 Participants
69. 2.5 Clinical Overview to Support Inclusion of Myocarditis & Pericarditis in Section 4.4 (Special Warnings and Precautions for use) of the Core Data Sheet, July 2021
70. Module 3.2.P.8.3 Stability Data, August 2021
71. Interim Report – BNT162b2 Booster (Dose 3): A Phase 1/2/3, Placebo Controlled, Randomized, Observer-Blind, Dose-Finding Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of SARS-CoV-2 RNA Vaccine Candidates Against COVID-19 in Healthy Individuals
72. Module 3.2.P.2.2 Drug Product – Tris-Sucrose, September 2021
73. Interim Report – Children 5 to <12 Years of Age: A Phase 1, Open-Label Dose-Finding Study to Evaluate Safety, Tolerability, and Immunogenicity and Phase 2/3 Placebo-Controlled, Observer-Blinded Safety, Tolerability, and Immunogenicity Study of a SARS-CoV-2 RNA Vaccine Candidate against COVID-19 in Healthy Children and Young Adults
74. Module 3.2.P.1 Description and Composition of the Drug Product – Tris-Sucrose, September 2021
75. Module 3.2.P.8.1 Stability Summary and Conclusion – Tris-Sucrose, September 2021
76. Module 3.2.P.3.5 Shipping Validation – Tris-Sucrose, September 2021
77. Module 3.2.P.2.6 Compatibility – Tris-Sucrose, September 2021
78. Module 3.2.P.2.3 Manufacturing Process Development – Process Development and Characterization – Tris/Sucrose, September 2021
79. Module 3.2.P.8.1 Stability Summary and Conclusions – Tris-Sucrose, November 2021
80. 2.5 Clinical Overview for Adult Booster Efficacy MAA – Study C4591031, November 2021
81. Interim Clinical Study Report, Protocol C4591001 – Interim Report – Adolescent 6-Month Update: A Phase 1/2/3, Placebo-Controlled, Randomized, Observer-Blind, Dose-Finding Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of SARS-CoV-2 RNA Vaccine Candidates Against COVID-19 in Healthy Individuals
82. Clinical Information Amendment – COVID-19 Vaccine C4591007 (5 to <12 Years) Efficacy Data in Phase 2/3 Study C4591007, October 2021

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83. Module 3.2.P.8.3 Stability Data, August 2021
84. 2.5 Clinical Overview – Pediatric (5-12 Years) Booster MAA Extension – April 2022

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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)

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)[64]

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

a. Source: Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2, by System Organ Class and Preferred Term – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 Subjects ≥16 Years of Age – Safety Population (Study C4591001, Cut-off 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 (Study C4591001, Cut-off 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 (Study C4591001, Cut-off date: 13March2021).
d. These adverse reactions were identified in the post-authorization period.

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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)[64]

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 (Study C4591001, Cut-off 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 (Study C4591001, Cut-off 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 (Study C4591001, Cut-off 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 and older (see Table A-1): angioedema, pruritus, malaise, lethargy, asthenia, decreased appetite, hyperhidrosis, and night sweats.

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Table A-3. Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency within each System Organ Class: Individuals 5 Through <12 Years of Age (06 September 2021 Data Cut-off Date)[64]

System Organ Class	ADR Term	Frequency n/N (%)
Blood and lymphatic system disorders	Lymphadenopathy	13/1518 (0.9%)[a]
Immune system disorders	Anaphylaxis[d]	Not known
	Hypersensitivity reactions	
	Rash[d]	5/1518 (0.3%)[a]
	Urticaria[d]	3/1518 (0.2%)[a]
	Pruritus[d]	1/1518 (0.1%)[a]
	Angioedema[d,e]	
Metabolism and nutrition disorders	Decreased appetite	1/1518 (0.1%)[a]
Nervous system disorders	Headache	579/1517 (38.2%)[b]
	Lethargy[e]	
Gastrointestinal disorders	Diarrhea[d]	146/1517 (9.6%)[b]
	Vomiting[d]	60/1517 (4.0%)[b]
	Nausea	6/1518 (0.4%)[a]
Skin and subcutaneous tissue disorders	Hyperhidrosis[e]	
	Night sweats[e]	
Musculoskeletal and connective tissue disorders	Myalgia (muscle pain)	266/1517 (17.5%)[b]
	Arthralgia (joint pain) (new)	115/1517 (7.6%)[b]
	Pain in extremity (arm)[d]	3/1518 (0.2%)[a]
General disorders and administration site conditions	Injection site pain	1279/1517 (84.3%)[c]
	Fatigue	785/1517 (51.7%)[b]
	Injection site redness	401/1517 (26.4%)[c]
	Injection site swelling	309/1517 (20.4%)[c]
	Chills	188/1517 (12.4%)[b]
	Pyrexia	126/1517 (8.3%)[b]
	Malaise	2/1518 (0.1%)[a]
	Asthenia[e]	

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

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Table A-4. Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency Within Each System Organ Class: BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) – Booster Safety Population (17 June 2021 Data Cut-off Date)[*,64]

System Organ Class	ADR Term	Frequency n/N (%)
Blood and lymphatic system disorders	Lymphadenopathy	16/306 (5.2%)[a,b]
Immune system disorders	Anaphylaxis[e]	Not known
	Hypersensitivity reactions	
	Rash[e]	1/306 (0.3%)[b]
	Pruritus[e,f]	
	Urticaria[e,f]	
	Angioedema[e,f]	
Metabolism and nutrition disorders	Decreased appetite	1/306 (0.3%)[b]
Nervous system disorders	Headache	140/289 (48.4%)[c]
	Lethargy[f]	
Gastrointestinal disorders	Diarrhea[e]	25/289 (8.7%)[c]
	Vomiting[e]	5/289 (1.7%)[c]
	Nausea	2/306 (0.7%)[b]
Skin and subcutaneous tissue disorders	Hyperhidrosis[f]	
	Night sweats[f]	
Musculoskeletal and connective tissue disorders	Myalgia (muscle pain)	113/289 (39.1%)[c]
	Arthralgia (joint pain) (new)	73/289 (25.3%)[c]
	Pain in extremity (arm)[e]	1/306 (0.3%)[b]
General disorders and administration site conditions	Injection site pain	240/289 (83.0%)[d]
	Fatigue	184/289 (63.7%)[c]
	Chills	84/289 (29.1%)[c]
	Pyrexia	25/289 (8.7%)[c]
	Injection site swelling	23/289 (8.0%)[d]
	Injection site redness	17/289 (5.9%)[d]
	Malaise[f]	
	Asthenia[f]	

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

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

b. Source: Number (%) of Subjects Reporting at Least 1 Adverse Event From Booster Dose to 1 Month After Booster Dose, by System Organ Class and Preferred Term – Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) – Booster Safety Population (Study C4591001, Cut-off date: 17June2021).

c. Source = Systemic Events, by Maximum Severity, Within 7 Days After Booster Dose Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) – Booster Safety Population (Study C4591001, Cut-off date: 17June2021).

d. Source = Local Reactions, by Maximum Severity, Within 7 Days After Booster Dose – Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) –Booster Safety Population (Study C4591001, Cut-off date: 17June2021).

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

f. The following events were not reported in the booster safety population in Study C4591001 but were reported in individuals ≥16 years of age following the 2-dose series (Cut-off date:13March2021) Table A-1: angioedema, pruritus, urticaria, malaise, lethargy, asthenia, hyperhidrosis, and night sweats.

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Table A-5. Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency Within Each System Organ Class: BNT162b2-Experienced Subjects (≥16 Years of Age) Who Received 1 Booster Dose of BNT162b2 (30 µg) in Study C4591031 – Booster Safety Population (5 October 2021 Data Cut-off Date)[64,80]

System Organ Class	ADR Term	Frequency n/N (%)
Blood and lymphatic system disorders	Lymphadenopathy[a]	135/5055 (2.8%)[b]
Immune system disorders	Anaphylaxis[c]	Not known
	Hypersensitivity reactions	
	Rash[c]	3/5055 (0.1%)[b]
	Pruritus[c]	3/5055 (0.1%)[b]
	Urticaria[c]	2/5055 (0.04%)[b]
	Angioedema[c,d]	
Metabolism and nutrition disorders	Decreased appetite	9/5055 (0.2%)[b]
Nervous system disorders	Headache[e]	
	Lethargy	12/5055 (0.2%)[b]
Gastrointestinal disorders	Diarrhea[c,e]	
	Vomiting[c,e]	
	Nausea	48/5055 (0.9%)[b]
Skin and subcutaneous tissue disorders	Night sweats	5/5055 (0.1%)[b]
	Hyperhidrosis	4/5055 (0.1%)[b]
Musculoskeletal and connective tissue disorders	Myalgia (muscle pain)[e]	
	Arthralgia (joint pain) (new)[e]	
	Pain in extremity (arm)[c]	54/5055 (1.1%)[b]
General disorders and administration site conditions	Injection site pain[e]	
	Fatigue[e]	
	Chills[e]	
	Pyrexia[e,f]	
	Injection site swelling[e]	
	Injection site redness[e]	
	Malaise	35/5055 (0.7%)[b]
	Asthenia	8/5055 (0.2%)[b]

a. A higher frequency of lymphadenopathy (2.8% vs. 0.4%) was observed in participants receiving a booster dose (in Study C4591031) compared to participants receiving 2 doses.
b. Source: Number (%) of Participants Reporting at Least 1 Adverse Event From Booster Vaccination to 1 Month After Booster Vaccination, by System Organ Class and Preferred Term – Blinded Follow-up Period – Safety Population (Study C4591031, Cut-off date: 05October2021).
c. These adverse reactions were identified in the post-authorization period.
d. The following event was not reported in the Study C4591031 but was reported in individuals ≥16 years of age 1 month after Dose 2 in Study C4591001 (Cut-off date: 13March2021): angioedema.
e. Please see Table A-4 for the frequency of the following reactogenicity adverse reactions that were reported in the booster safety population of Study C4591001: headache, diarrhea, vomiting, myalgia (muscle pain), arthralgia (joint pain) (new), injection site pain, fatigue, chills, pyrexia, injection site swelling, injection site redness.
f. The preferred term pyrexia is a cluster term also covering 'body temperature increased'.

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Table A-6. Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency Within Each System Organ Class: Individuals 5 Through <12 Years of Age Who Received a Booster Dose (Dose 3) of BNT162b2 (22March2022 Data Cut-off Date)[*,64,84]

System Organ Class	ADR Term	Frequency n/N (%)
Blood and lymphatic system disorders	Lymphadenopathy[a]	10/401 (2.5%)[b]
Immune system disorders	Anaphylaxis[e]	Not known
	Hypersensitivity reactions	
	Rash[e]	1/401 (0.2%)[b]
	Urticaria[e,f]	
	Pruritus[e,f]	
	Angioedema[e,f]	
Metabolism and nutrition disorders	Decreased appetite[f]	
Nervous system disorders	Headache	126/371 (34.0%)[c]
	Lethargy[f]	
Gastrointestinal disorders	Diarrhea[e]	18/371 (4.9%)[c]
	Vomiting[e]	9/371 (2.4%)[c]
	Nausea[f]	
Skin and subcutaneous tissue disorders	Hyperhidrosis[f]	
	Night sweats[f]	
Musculoskeletal and connective tissue disorders	Myalgia (muscle pain)	68/371 (18.3%)[c]
	Arthralgia (joint pain) (new)	25/371 (6.7%)[c]
	Pain in extremity (arm)[e,f]	
General disorders and administration site conditions	Injection site pain	274/371 (73.9%)[d]
	Fatigue	169/371 (45.6%)[c]
	Injection site swelling	61/371 (16.4%)[d]
	Injection site redness	58/371 (15.6%)[d]
	Chills	39/371 (10.5%)[c]
	Pyrexia	25/371 (6.7%)[c]
	Malaise[f]	
	Asthenia[f]	

* Booster dose (Dose 3) of BNT162b2 10 µg was administered to participants 5 through <12 years of age in Study C4591007.

a. A higher frequency of lymphadenopathy was observed in participants 5 through <12 years of age in Study C4591007 (2.5% vs. 0.9%) receiving a booster dose compared to participants receiving 2 doses. The frequency of lymphadenopathy was calculated as follows: lymphadenopathy (n = 8), lymph node palpable (n = 1), axillary mass (n = 1) (8+1+1 = 10/401 = 2.5%).

b. Source: Number (%) of Participants Reporting at Least 1 Adverse Event From Dose 3 to 1 Month After Dose 3, by System Organ Class and Preferred Term – Phase 2/3 – Participants Who Received Dose 3 of BNT162b2 – 5 to <12 Years of Age – Safety Population (Study C4591007, Cut-off date: 22March2022).

c. Source = Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Phase 2/3 – Participants Who Received Dose 3 of BNT162b2 – 5 to <12 Years of Age – Safety Population (Study C4591007, Cut-off date: 22March2022).

d. Source = Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Phase 2/3 – Participants Who Received Dose 3 of BNT162b2 – 5 to <12 Years of Age – Safety Population (Study C4591007, Cut-off date: 22March2022).

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

f. The following events were not reported in participants 5 through <12 years of age in Study C4591007 after Dose 3 but were reported in individuals 16 years of age and older from Dose 1 to 1 month after Dose 2 in Study C4591001 (see Table A-1): urticaria, pruritus, angioedema, decreased appetite, lethargy, nausea, night sweats, hyperhidrosis, pain in extremity (arm), malaise, asthenia.

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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

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)[64]

System Organ Class	Very Common ≥1/10 (≥10%)	Common ≥1/100 to <1/10 (≥1% to <10%)	Uncommon ≥1/1,000 to <1/100 (≥0.1% to <1%)	Rare ≥1/10,000 to <1/1,000 (≥0.01% to <0.1%)	Very Rare <1/10,000 (<0.01%)	Frequency not known (cannot be estimated from the available data)
Blood and lymphatic system disorders			Lymphadenopathy			
Immune system disorders			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			

*. CIOMS frequency categories are based on clinical trial C4591001 crude incidence and was reported to only one significant figure.
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.

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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)[64]

System Organ Class	Very Common ≥1/10 (≥10%)	Common ≥1/100 to <1/10 (≥1% to <10%)	Uncommon ≥1/1,000 to <1/100 (≥0.1% to <1%)	Rare ≥1/10,000 to <1/1,000 (≥0.01% to <0.1%)	Very Rare <1/10,000 (<0.01%)	Frequency not known (cannot be estimated from the available data)
Blood and lymphatic system disorders			Lymphadenopathy			
Immune system disorders			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				

*. CIOMS frequency categories are based on clinical trial C4591001 crude incidence and was reported to only one significant figure.

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

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

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Table B-3. ADRs by System Organ Class and CIOMS Frequency Category* Listed in Order of Decreasing Medical Seriousness Within Each Frequency Category and System Organ Class: Individuals 5 Through <12 Years of Age (06 September 2021 Data Cut-off Date)[64]

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

*. CIOMS frequency categories are based on clinical trial C4591007 crude incidence and was reported to only one significant figure.

a. These adverse reactions were identified in the post-authorization period. The following events were not reported in participants 5 through <12 years of age in Study C4591007 but were reported in individuals 16 years of age and older in Study C4591001 (see Table B-1): angioedema, lethargy, asthenia, hyperhidrosis, and night sweats.

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

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Table B-4. ADRs by SOC and CIOMS Frequency Category* Listed in Order of Decreasing Medical Seriousness Within Each Frequency Category and SOC: BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) – Booster Safety Population (17 June 2021 Data Cut-off Date)†,[64]

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

*. CIOMS frequency categories are based on clinical trial C4591001 crude incidence and was reported to only one significant figure.

† The booster dose of BNT162b2 30 µg was administered to participants 18 to 55 years of age.

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

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Table B-5. ADRs by System Organ Class and CIOMS Frequency Category* Listed in Order of Decreasing Medical Seriousness Within Each Frequency Category and System Organ Class: Study C4591031† (5 October 2021 Data Cut-off Date)[64]

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

* CIOMS frequency categories are based on clinical trial C4591031 crude incidence and was reported to only one significant figure.

† Study C4591031 included individuals 16 years of age and older.

Please see Table B-4 for the CIOMS Frequency Categories for the following reactogenicity adverse reactions that were reported in the booster safety population of Study C4591001: headache, diarrhea, vomiting, myalgia (muscle pain), arthralgia (joint pain) (new), injection site pain, fatigue, chills, pyrexia, injection site swelling, injection site redness.

The preferred term pyrexia is a cluster term also covering 'body temperature increased'.

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

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

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Table B-6. ADRs by System Organ Class and CIOMS Frequency Category* Listed in Order of Decreasing Medical Seriousness Within Each Frequency Category and System Organ Class: Individuals 5 Through <12 Years of Age Who Received Dose 3 (22March2022 Data Cut-off Date)†,64,84

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

* CIOMS frequency categories are based on clinical trial C4591007 crude incidence and was reported to only one significant figure.

† Dose 3 (a booster dose) of BNT162b2 10 µg was administered to participants 5 through <12 years of age in Study C4591007.

a. These adverse reactions were identified in the post-authorization period. The following events were not reported in participants 5 through <12 years of age in Study C4591007 after Dose 3 but were reported in individuals 16 years of age and older from Dose 1 to 1 month after Dose 2 in Study C4591001 (see **Error! Reference source not found.**): urticaria, pruritus, angioedema, decreased appetite, lethargy, nausea, night sweats, hyperhidrosis, pain in extremity (arm), malaise, and asthenia.

b. The following event is categorized as a hypersensitivity reaction: rash.

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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.

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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

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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 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.

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PREPARED BY PFIZER INC

CDS EFFECTIVE DATE: 26-JULY-2022

Date of Superseded CDS: 10-May-2022

COVID-19 mRNA Vaccine

CORE DATA SHEET

VERSION 14

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1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION[1,2,72,85]

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

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

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

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

For the full list of excipients, see Section 6.1.

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

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

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

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

For the full list of excipients, see Section 6.1.

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

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

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

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

For the full list of excipients, see Section 6.1.

*[Editorial guidance for countries: Select this text for the **Tris/Sucrose presentation, 3 micrograms/dose**.]*

TRADENAME (for age 6 months to <5 years): This is a multidose vial and must be diluted before use. One vial (0.4 mL) contains 10 doses of 0.2 mL after dilution (see Sections 4.2 and 6.6).

One dose (0.2 mL) contains 3 micrograms of COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

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

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM[2,3,72,85]

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

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

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

TRADENAME (Do Not Dilute): Dispersion for injection.

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

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

*[Editorial guidance for countries: Select this text for the **Tris/Sucrose presentation, 3 micrograms/dose**.]*

TRADENAME (for age 6 months to <5 years): Concentrate for dispersion for injection.

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

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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 6 months of age and older.[4,49,73,86]

4.2. Posology and method of administration

Posology

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

Individuals 12 years of age and older

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

Booster dose in individuals 16 years of age and older

A booster dose of TRADENAME (Dilute Before Use) and TRADENAME (Do Not Dilute) may be administered intramuscularly at least 5 months after the second dose in individuals 16 years of age and older.[71,87]

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

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

Interchangeability

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

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

For further information on efficacy, see Section 5.1.

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

Individuals 5 through <12 years of age

TRADENAME (for age 5 years to <12 years) is administered intramuscularly after dilution as a primary series of 2 doses (0.2 mL) at greater than or equal to 21 days (preferably 3 weeks) apart.[73]

Booster dose in individuals 5 through <12 years of age

A booster dose of TRADENAME (for age 5 years to <12 years of age) may be administered intramuscularly at least 6 months after the second dose in individuals 5 years through <12 years of age.[84]

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

Interchangeability

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

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

For further information on efficacy, see Section 5.1.

*[Editorial guidance for countries: Select this text for the **Tris/Sucrose presentation, 3 micrograms/dose**.]*

Individuals 6 months through <5 years of age

TRADENAME (for age 6 months to <5 years) is administered intramuscularly after dilution as a primary series of 3 doses (0.2 mL). The initial 2 doses are administered 3 weeks apart followed by a third dose administered at least 8 weeks after the second dose.[86]

Individuals who will turn from 4 years to 5 years of age between their doses in the vaccination series should receive their age-appropriate dose at the time of the vaccination and the interval between doses is determined by the individual's age at the start of the vaccination series.[88]

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TRADENAME (for age 6 months to <5 years) cannot be used in individuals 5 years of age and older.

Interchangeability

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

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

For further information on efficacy, see Section 5.1.

Pediatric population

The safety and efficacy of TRADENAME in individuals under 6 months of age have not yet been established. The safety and effectiveness of a booster dose of TRADENAME in individuals 16 through 17 years of age is based on safety and effectiveness data in adults at least 18 through 55 years of age.[71,86]

Geriatric population

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

The safety of a booster dose of TRADENAME in individuals 65 years of age and older is based on safety data in 12 booster dose recipients 65 through 85 years of age in Study 2, 306 booster dose recipients 18 through 55 years of age in Study 2, and 1,175 booster dose recipients 65 years of age and older in Study 4. The effectiveness of a booster dose of TRADENAME in individuals 65 years of age and older is based on effectiveness data in 306 booster dose recipients 18 through 55 years of age in Study 2, and an efficacy analysis from participants 16 years of age and older in 9,945 participants in Study 4.[71, 80]

Method of administration

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

Administer TRADENAME intramuscularly in the deltoid muscle.

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

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

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Individuals 12 years of age and older

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

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

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

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

Administer TRADENAME intramuscularly in the deltoid muscle.

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

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

Individuals 12 years of age and older

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

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

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

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

Administer TRADENAME intramuscularly in the deltoid muscle.

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

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

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Individuals 5 through <12 years of age

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

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

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

*[Editorial guidance for countries: Select this text for the **Tris/Sucrose presentation, 3 micrograms/dose**.]*

In individuals 6 to less than 12 months of age, administer TRADENAME intramuscularly in the anterolateral aspect of the thigh. In individuals 1 years of age and older, administer TRADENAME intramuscularly in the anterolateral aspect of the thigh or the deltoid muscle.

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

After dilution, vials of TRADENAME (for age 6 months to <5 years) contains 10 doses of 0.2 mL of vaccine.

Individuals 6 months through <5 years of age

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

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

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

4.3. Contraindications

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

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4.4. Special warnings and precautions for use

Traceability

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

General recommendations

As with all injectable vaccines, appropriate medical treatment and supervision must always be readily available in case of a rare anaphylactic event following the administration of the vaccine.[9]

Very rare cases of myocarditis and pericarditis have been reported following vaccination with TRADENAME. Typically, the cases have occurred more often in younger men and after the second dose of the vaccine and within 14 days after vaccination. Based on accumulating data, the reporting rates of myocarditis and pericarditis after primary series in children ages 5 through <12 years are lower than in ages 12 through 17 years. Rates of myocarditis and pericarditis in booster doses do not appear to be higher than after the second dose in the primary series. The cases are generally mild and individuals tend to recover within a short time following standard treatment and rest. Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis in vaccine recipients.[69,89]

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.

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4.6. Fertility, pregnancy and lactation

Pregnancy

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

Lactation

It is unknown whether TRADENAME is excreted in human milk.

Fertility

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

4.7. Effects on ability to drive and use machines

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

4.8. Undesirable effects

Summary of safety profile

The safety of TRADENAME was evaluated in participants 5 years of age and older in 3 clinical studies conducted in the United States, Europe, Turkey, South Africa, and South America.[12,49] Study BNT162-01 (Study 1) enrolled 60 participants, 18 through 55 years of age and 36 participants, 56 through 85 years of age.[68] Study C4591001 (Study 2) enrolled approximately 46,000 participants,[41] 12 years of age or older.[12] Study C4591007 (Study 3) enrolled approximately 2,300 participants 5 through <12 years of age.[73] Study 3 also enrolled approximately 1,800 participants 2 through 4 years of age and 1,200 participants 6 months through 23 months of age.[86]
Additionally, 306 existing Phase 3 participants at least 18 through 55 years of age received a booster dose of TRADENAME approximately 6 months after the second dose in the non-placebo-controlled booster dose portion of Study 2. The overall safety profile for the booster dose was similar to that seen after 2 doses.[71]

In Study C4591031 (Study 4), a placebo-controlled booster study, 5,081 participants 16 years of age and older were recruited from Study 2 to receive a booster dose of TRADENAME at least

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6 months after the second dose. The overall safety profile for the booster dose was similar to that seen after 2 doses.[80]

In a subset of Study 3 (Phase 2/3) participants, 401 participants 5 through <12 years of age received a booster dose of TRADENAME at least 5 months after completing the primary series. The overall safety profile for the booster dose was similar to that seen after the primary series.[84]

Participants 16 years of age and older – after 2 doses

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

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

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

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

Adolescents 12 through 15 years of age – after 2 doses[81]

In an analysis of long-term safety follow-up in Study 2, 2,260 adolescents (1,131 TRADENAME; 1,129 placebo) were 12 through 15 years of age. Of these, 1,559 adolescents (786 TRADENAME and 773 placebo) have been followed for ≥4 months after the second dose.[41,42] The safety evaluation in Study 2 is ongoing.

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

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

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

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

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Children 2 through 4 years of age – after 3 doses[90,91,92]

In an analysis of Study 3 (Phase 2/3), 2,750 individuals (1,835 TRADENAME 3 mcg and 915 placebo) were 2 through 4 years age. Based on data in the blinded placebo-controlled follow-up period up to the cutoff date of April 29, 2022, 886 individuals 2 through 4 years of age who received a 3-dose primary course (606 TRADENAME 3 mcg and 280 placebo) have been followed a median of 1.4 months after the third dose.

The most frequent adverse reactions in children 2 through 4 years of age that received any primary series dose included pain at injection site and fatigue (>40%), injection site redness and fever (>10%).

Children 6 through 23 months of age – after 3 doses[93,94,95]

In an analysis of Study 3 (Phase 2/3), 1,776 individuals (1,178 TRADENAME 3 mcg and 598 placebo) were 6 through 23 months of age. Based on data in the blinded placebo-controlled follow-up period up to the cutoff date of April 29, 2022, 570 individuals 6 through 23 months of age who received a 3-dose primary course (386 TRADENAME 3 mcg and 184 placebo) have been followed for a median of 1.3 months after the third dose.

The most frequent adverse reactions in children 6 through 23 months of age that received any primary series dose included irritability (>60%), decrease appetite (>30%), tenderness at the injection site (>20%), injection site redness and fever (>10%).

Participants 16 years of age and older – after booster dose[71]

A subset from Study 2 (Phase 2/3) participants of 306 adults at least 18 through 55 years of age who completed the primary TRADENAME 2-dose course, received a booster dose of TRADENAME approximately 6 months (range of 4.8 to 8.0 months) after receiving Dose 2. Of these, 301 participants have been followed for ≥4 months after the booster dose of TRADENAME.[96]

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

In Study 4, a placebo-controlled booster study, participants 16 years of age and older recruited from Study 2 received a booster dose of TRADENAME (5,081 participants), or placebo (5,044 participants) at least 6 months after the second dose of TRADENAME. Overall, participants who received a booster dose, had a median follow-up time of 2.8 months (range 0.3 to 7.5 months) after the booster dose in the blinded placebo-controlled follow-up period to the cut-off date (8 February 2022).[80,97] Of these, 1281 participants (895 TRADENAME and 386 placebo) have been followed for ≥4 months after the booster dose of TRADENAME.[98]

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Children 5 through <12 years of age – after booster dose[84]

In a subset from Study 3, a total of 401 children 5 through <12 years of age received a booster dose of TRADENAME 10 mcg at least 5 months (range of 5 to 9 months) after completing the primary series. The analysis of the Study 3 (Phase 2/3) subset is based on data up to the cut-off date of March 22, 2022 (median follow-up time of 1.3 months).

The most frequent adverse reactions in participants 5 through <12 years of age were injection site pain (>70%), fatigue (>40%), headache (>30%), myalgia, chills, injection site redness, and swelling (>10%).

Table 1. Adverse Drug Reactions[13,14,16,64,80,86]

System Organ Class	Adverse Drug Reactions
Blood and lymphatic system disorders	Lymphadenopathy[a]
Metabolism and nutrition disorders	Decreased appetite
Psychiatric disorders	Irritability[c]
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[b] Chills Asthenia Malaise Fatigue Injection site pain Injection site tenderness[c] Injection site swelling Injection site redness

a. A higher frequency of lymphadenopathy was observed in participants 5 through <12 years of age in Study 3 (2.5% vs. 0.9%) and in participants 16 years of age and older in Study 4 (2.8% vs. 0.4%) receiving a booster dose compared to participants receiving 2 doses.[71,84]
b. A higher frequency of pyrexia was observed after the second dose compared to the first dose. The preferred term pyrexia is a cluster term covering also body temperature increased.
c. Irritability and injection site tenderness pertain to participants 6 through 23 months of age.[86]

Adverse reactions from TRADENAME post-authorization experience

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

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Table 2. Adverse Drug Reactions[38,64,80,89]

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

a. A higher frequency of pain in extremity (1.1% vs. 0.8%) was observed in participants receiving a booster dose in Study 4 compared to participants receiving 2 doses.

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

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worsening disease during the 6 weeks before enrollment,[21] were included as were participants with known stable infection with HIV, hepatitis C virus (HCV), or hepatitis B virus (HBV).[12]

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

In the Phase 2/3 portion of Study 2, based on data accrued through 14 November 2020, approximately 44,000 participants 12 years of age and older were randomized equally and received 2 doses of TRADENAME 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 TRADENAME 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)

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	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)

At the time of the primary efficacy analysis, participants had been followed for symptomatic COVID-19 for at least 2214 person-years for the TRADENAME 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.

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Table 4. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Age Subgroup – Participants Without Evidence of Infection and Participants With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

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

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting).
Abbreviations: NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.

* Participants who had no evidence of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

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

b. n1 = Number of participants meeting the endpoint definition.

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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 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. 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]

	TRADENAME N[a]=18,198	Placebo N[a]=18,325	
Subgroup	Cases n1[b] Surveillance Time[c] (n2[d])	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.

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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)

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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.

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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)
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)

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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 1,000 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)

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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]
Country			
Argentina	16 1.033 (2655)	110 1.017 (2670)	85.7 (75.7, 92.1)
Brazil	14 0.441 (1419)	82 0.408 (1401)	84.2 (71.9, 91.7)
Germany	0 0.047 (237)	1 0.048 (243)	100.0 (-3868.6, 100.0)
South Africa	0 0.099 (358)	10 0.096 (358)	100.0 (56.6, 100.0)
Turkey	0 0.029 (238)	6 0.026 (232)	100.0 (22.2, 100.0)
United States	51 4.861 (16,735)	664 4.678 (16,785)	92.6 (90.2, 94.6)

Notes: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting). Included confirmed cases in participants 12 through 15 years of age: 0 in the TRADENAME group; 18 in the placebo group.

* Participants who had no evidence of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

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.

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Table 9. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – Participants Without Evidence of Infection* Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population[23]

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

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c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
f. At risk is defined as having at least 1 of the Charlson Comorbidity Index (CMI) category or obesity (BMI ≥30 kg/m^2).
g. Obese is defined as BMI ≥30 kg/m^2.

The updated subgroup analyses of vaccine efficacy by risk status in participants followed up to 6 months after Dose 2 (with a cut-off date of 13 March 2021) are presented in Table 10 and Table 11.

Table 10. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – Participants Without Evidence of Infection* Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period[55]

Subgroup	TRADENAME N[a]=20,998 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=21,096 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]
First COVID-19 occurrence from 7 days after Dose 2[f]	77 6.247 (20,712)	850 6.003 (20,713)	91.3 (89.0, 93.2)
At risk[g]			
Yes	35 2.797 (9167)	401 2.681 (9136)	91.6 (88.2, 94.3)
No	42 3.450 (11,545)	449 3.322 (11,577)	91.0 (87.6, 93.6)
Age group (years) and risk status			
16 through 64 and not at risk	41 2.776 (8887)	385 2.661 (8886)	89.8 (85.9, 92.8)
16 through 64 and at risk	29 2.083 (6632)	325 1.993 (6629)	91.5 (87.5, 94.4)
65 and older and not at risk	1 0.553 (1870)	53 0.546 (1922)	98.1 (89.2, 100.0)
65 and older and at risk	6 0.680 (2322)	71 0.656 (2304)	91.8 (81.4, 97.1)
Obese[h]			
Yes	27 2.103 (6796)	314 2.050 (6875)	91.6 (87.6, 94.6)
No	50 4.143 (13,911)	536 3.952 (13,833)	91.1 (88.1, 93.5)

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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]
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.

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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)

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.

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

Efficacy against severe COVID-19 - after 2 doses

Secondary efficacy analyses suggested benefit of TRADENAME 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 TRADENAME group and 9 cases in placebo group), with an estimated vaccine efficacy of 75.0% (95% CI: -152.6, 99.5) (1 case in TRADENAME 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 TRADENAME 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)

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

Efficacy and immunogenicity in adolescents 12 to 15 years of age – after 2 doses

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

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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 through 25 years of age who had no serological or virological evidence of past SARS-CoV-2 infection. The immune response to TRADENAME in adolescents 12 to 15 years of age (n=190) was non-inferior to the immune

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response in participants 16 through 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 through 25 years of age group was 1.76, with a 2-sided 95% CI of 1.47 to 2.10, meeting the 1.5-fold non-inferiority criterion (the lower bound of the 2-sided 95% CI for the 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 through 25 years of age.[48]

An updated efficacy analysis of Study 2 has been performed in approximately 2,260 adolescents 12 through 15 years of age evaluating confirmed COVID-19 cases accrued up to a data cut-off date of September 2, 2021, representing up to 6 months of follow-up after Dose 2 for participants in the efficacy population.[81]

The updated vaccine efficacy information in adolescents 12 through 15 years of age is presented in Table 14.

Table 14. 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 Through 15 Years of Age Evaluable Efficacy (7 Days) Population[81]

First COVID-19 occurrence from 7 days after Dose 2 in adolescents 12 through 15 years of age without evidence of prior SARS-CoV-2 infection*			
	TRADENAME N[a]=1057 Cases n1[b] Surveillance Time[c] (n2[d])	**Placebo N[a]=1030 Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI[e])**
Adolescents 12 through 15 years of age	0 0.343 (1043)	28 0.322 (1019)	100.0 (86.8, 100.0)
First COVID-19 occurrence from 7 days after Dose 2 in adolescents 12 through 15 years of age with or without evidence of prior SARS-CoV-2 infection			
	TRADENAME N[a]=1119 Cases n1[b] Surveillance Time[c] (n2[d])	**Placebo N[a]=1109 Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI[e])**
Adolescents 12 through 15 years of age	0 0.362 (1098)	30 0.345 (1088)	100.0 (87.5, 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).

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* 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.

Efficacy in children 5 through <12 years of age – after 2 doses

A descriptive efficacy analysis of Study 3 has been performed in 1,968 children 5 through <12 years of age without evidence of infection prior to 7 days after Dose 2. This analysis evaluated confirmed symptomatic COVID-19 cases accrued up to a data cut-off date of October 8, 2021.[82]

Table 15 presents the specific demographic characteristics in participants who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose.

Table 15. Demographics Characteristics – Participants Without Evidence of Infection Prior to 7 Days After Dose 2 – Phase 2/3 – 5 Through <12 Years of Age – Evaluable Efficacy Population[82]

	TRADENAME 10 mcg/dose (N[a]=1305) n[b] (%)	**Placebo (N[a]=663) n[b] (%)**
Sex		
Male	679 (52.0)	343 (51.7)
Female	626 (48.0)	320 (48.3)
Age at Vaccination		
Mean (SD)	8.2 (1.93)	8.1 (1.98)
Median	8.0	8.0
Min, max	(5, 11)	(5, 11)
Race		
White	1018 (78.0)	514 (77.5)
Black or African American	76 (5.8)	48 (7.2)
American Indian or Alaska Native	<1.0%	<1.0%
Asian	86 (6.6)	46 (6.9)
Native Hawaiian or other Pacific Islander	<1.0%	<1.0%
Other[c]	110 (8.4)	52 (7.8)

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	TRADENAME 10 mcg/dose (N[a]=1305) n[b] (%)	Placebo (N[a]=663) n[b] (%)
Ethnicity		
Hispanic or Latino	243 (18.6)	130 (19.6)
Not Hispanic or Latino	1059 (81.1)	533 (80.4)
Not reported	<1.0%	<1.0%
Comorbidities[d]		
Yes	262 (20.1)	133 (20.1)
No	1043 (79.9)	530 (79.9)

a. N = number of participants in the specified group from the evaluable efficacy population with no evidence of SARS CoV-2 infection prior to 7 days after Dose 2. This value is the denominator for the percentage calculations. Evaluable efficacy population included all eligible randomized participants who received all vaccination(s) as randomized within the predefined window, had no other important protocol deviations as determined by the clinician.
b. n = Number of participants with the specified characteristic.
c. Includes multiracial and not reported.
d. Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as participants who had at least 1 of the prespecified comorbidities based on MMWR 69(32);1081-1088 and/or obesity (BMI ≥95th percentile).

The descriptive vaccine efficacy results in children 5 through <12 years of age without evidence of prior SARS-CoV-2 infection are presented in Table 16. None of the cases accrued met criteria for severe COVID-19 or multisystem inflammatory syndrome in children (MIS-C). No cases of COVID-19 were observed in either the vaccine group or the placebo group in participants with evidence of prior SARS-CoV-2 infection.[82]

Table 16. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2: Without Evidence of Infection Prior to 7 Days After Dose 2 – Phase 2/3 – Children 5 Through <12 Years of Age Evaluable Efficacy Population[82]

First COVID-19 occurrence from 7 days after Dose 2 in children 5 through <12 years of age without evidence of prior SARS-CoV-2 infection*			
	TRADENAME 10 mcg/dose N[a]=1305 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=663 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)
Children 5 through 11 years of age	3 0.322 (1273)	16 0.159 (637)	90.7 (67.7, 98.3)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting).
* Participants who had no evidence of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
a. N = Number of participants in the specified group.

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b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1,000 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.

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

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

In Study 3, an analysis of SARS-CoV-2 50% neutralizing titers (NT50) 1 month after Dose 2 in a randomly selected subset of participants demonstrated effectiveness by immunobridging of immune responses comparing children 5 through <12 years of age in the Phase 2/3 part of Study 3 to participants 16 through 25 years of age in the Phase 2/3 part of Study 2 who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2, meeting the prespecified immunobridging criteria for both the GMR and the seroresponse difference with seroresponse defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from baseline (before Dose 1).

The ratio of the SARS-CoV-2 NT50 in children 5 through <12 years of age to that of young adults 16 through 25 years of age was 1.04 (2-sided 95% CI: 0.93, 1.18), as presented in Table 17.

Table 17. Summary of Geometric Mean Ratio for 50% Neutralizing Titer – Comparison of Children 5 Through <12 Years of Age (Study 3) to Participants 16 Through 25 Years of Age (Study 2) – Participants Without* Evidence of Infection up to 1 Month After Dose 2 – Dose 2 Evaluable Immunogenicity Population[73]

		TRADENAME			
		10 mcg/Dose 5 Through <12 Years n^a=264	30 mcg/Dose 16 Through 25 Years n^a=253	5 Through <12 Years/ 16 Through 25 Years	
Assay	Time Point[b]	GMT[c] (95% CI[c])	GMT[c] (95% CI[c])	GMR[d] (95% CI[d])	Met Immunobridging Objective[e] (Y/N)
SARS-CoV-2 neutralization assay - NT50 (titer)[f]	1 month after Dose 2	1197.6 (1106.1, 1296.6)	1146.5 (1045.5, 1257.2)	1.04 (0.93, 1.18)	Y

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

* Participants who had no serological or virological evidence (up to 1 month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and 1 month after Dose 2, SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT (nasal swab) at any

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unscheduled visit up to 1 month after Dose 2 blood collection) and had no medical history of COVID-19 were included in the analysis.

a. n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
b. Protocol-specified timing for blood sample collection.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
d. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titers (Group 1[5 through <12 years of age] - Group 2 [16 through 25 years of age]) and the corresponding CI (based on the Student t distribution).
e. Immunobridging is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥0.8.
f. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, 99.2% of children 5 through <12 years of age and 99.2% of participants 16 through 25 years of age had a seroresponse from before vaccination to 1 month after Dose 2. The difference in proportions of participants who had seroresponse between the 2 age groups (children – young adult) was 0.0% (2-sided 95% CI: -2.0%, 2.2%), as presented in Table 18.

Table 18. Difference in Percentages of Participants With Seroresponse – Participants Without* Evidence of Infection up to 1 Month After Dose 2 – Immunobridging Subset – Phase 2/3 – Comparison of 5 Through <12 Years of Age to Study 2 Phase 2/3 16 Through 25 Years of Age – Evaluable Immunogenicity Population[73]

		TRADENAME			
		Study 3 10 mcg/Dose 5 Through <12 Years N[a]=264	Study 2 30 mcg/Dose 16 Through 25 Years N[a]=253	5 Through <12 Years / 16 Through 25 Years	
Assay	Time Point[b]	n[c] (%) (95% CI[d])	n[c] (%) (95% CI[d])	Difference %[e] (95% CI[f])	Met Immunobridging Objective[g] (Y/N)
SARS-CoV-2 neutralization assay - NT50 (titer)[h]	1 month after Dose 2	262 (99.2) (97.3, 99.9)	251 (99.2) (97.2, 99.9)	0.0 (-2.0, 2.2)	Y

Abbreviations: LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer 50; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result ≥4 × LLOQ is considered a seroresponse.

* Participants who had no serological or virological evidence (up to 1 month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and 1 month after Dose 2, SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT (nasal swab) at any unscheduled visit up to 1 month after Dose 2 blood collection) and had no medical history of COVID-19 were included in the analysis.

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a. N = number of participants with valid and determinate assay results both before vaccination and at 1 month after Dose 2. These values are the denominators for the percentage calculations.
b. Protocol-specified timing for blood sample collection.
c. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.
d. Exact 2-sided CI based on the Clopper and Pearson method.
e. Difference in proportions, expressed as a percentage (Group 1 [5 through <12 years of age] – Group 2 [16 through 25 years of age]).
f. 2-Sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
g. Immunobridging is declared if the lower bound of the 2-sided 95% CI for the difference in proportions is greater than -10.0%.
h. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

Efficacy and immunogenicity in individuals 6 months through <5 years of age – 3-dose primary course[86]

A descriptive efficacy analysis was performed across the combined population of participants 6 months through <5 years of age based on cases confirmed among 992 participants in the TRADENAME group and 464 participants in the placebo group who received all 3 doses of study intervention during the blinded follow-up period. The observed vaccine efficacy from at least 7 days after Dose 3 to the cutoff date (29 April 2022) was 80.3% (2-sided 95% CI: 13.9, 96.7) based on 3 cases in the TRADENAME group and 7 cases in the placebo group, adjusted for surveillance time (noting 2:1 randomization ratio).

Children 2 through 4 years of age – after 3 doses[86]
A descriptive efficacy analysis of Study 3 has been performed in participants 2 through 4 years of age. This analysis evaluated confirmed symptomatic COVID-19 cases accrued up to a data cutoff date of 29 April 2022.

Table 19 presents the specific demographic characteristics in participants 2 through 4 years of age who received 3 doses of TRADENAME (3 mcg modRNA) or placebo.

Table 19. Demographics Characteristics – Phase 2/3 – Participants 2 Through 4 Years of Age – Dose 3 All-Available Efficacy Population[99]

	TRADENAME 3 mcg/Dose (N[a]=606) n[b] (%)	**Placebo (N[a]=280) n[b] (%)**
Sex		
Male	290 (47.9)	124 (44.3)
Female	316 (52.1)	156 (55.7)
Age at Vaccination (years)		
Mean (SD)	2.9 (0.77)	2.9 (0.75)
Median	3.0	3.0
Min, max	(2, 4)	(2, 4)

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	TRADENAME 3 mcg/Dose (N[a]=606) n[b] (%)	Placebo (N[a]=280) n[b] (%)
Race		
White	455 (75.1)	219 (78.2)
Black or African American	29 (4.8)	13 (4.6)
American Indian or Alaska Native	0	2 (0.7)
Asian	64 (10.6)	26 (9.3)
Native Hawaiian or other Pacific Islander	1 (0.2)	0
Other[c]	57 (9.4)	20 (7.1)
Ethnicity		
Hispanic or Latino	77 (12.7)	36 (12.9)
Not Hispanic or Latino	528 (87.1)	244 (87.1)
Not reported	1 (0.2)	0
Comorbidities[d]		
Yes	71 (11.7)	42 (15.0)
No	535 (88.3)	238 (85.0)

Abbreviations: BMI = body mass, SD = standard deviation.

a. N = Number of participants in the specified group from the Dose 3 all-available efficacy population. This value is the denominator for the percentage calculations. Dose 3 all-available efficacy population included all randomized participants who received 3 doses of TRADENAME (3 mcg modRNA) or placebo.
b. n = Number of participants with the specified characteristic.
c. Includes multiracial and not reported.
d. Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as participants who had at least 1 of the prespecified comorbidities based on Morbidity and Mortality Weekly Report 69(32);1081-1088 and/or obesity (BMI ≥95th percentile).

The descriptive vaccine efficacy results after Dose 3 in participants 2 through 4 years of age are presented in Table 20.

Table 20. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 3 - Phase 2/3 – Participants 2 Through 4 Years of Age – Dose 3 All-available Efficacy Population (Blinded Follow-up Period)[100]

	TRADENAME 3 mcg/Dose N[a]=606 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=280 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy (%) (95% CI[e])
First COVID-19 occurrence from 7 days after Dose 3	2 0.056 (481)	5 0.025 (209)	82.3 (-8.0, 98.3)

Abbreviation: VE = vaccine efficacy.

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

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shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting; inability to eat/poor feeding).

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 3 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Two-sided 95% confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.

Additional evaluation of vaccine efficacy for cases confirmed at least 7 days after Dose 2 and before Dose 3 was performed. In the evaluable efficacy population in participants without prior evidence of SARS-CoV-2 infection before or during the vaccination regimen the observed vaccine efficacy from at least 7 days after Dose 2 and before Dose 3 was 35.9% (2-sided 95% CI: 11.0%, 53.7%). The vaccine efficacy in participants with or without prior evidence of SARS-CoV-2 infection before or during the vaccination regimen was similar.

Analysis of COVID-19 cases that excluded those involving coinfection with other respiratory pathogens did not meaningfully impact the estimated vaccine efficacy in this population.

Severe COVID-19 criteria (as described in the protocol, based on FDA definition and modified for children) were fulfilled for 7 cases (6 TRADENAME and 1 placebo) among participants 2 through 4 years of age, of which 5 of the 6 cases in the TRADENAME group fulfilled a single criterion of increased heart rate or respiratory rate and 1 case in the placebo group fulfilled a single criterion of decreased peripheral oxygen saturation (88% on room air). None of the cases accrued met criteria for multisystem inflammatory syndrome in children (MIS-C).

Immunogenicity analyses have been performed in the immunobridging subset of 143 Study 3 participants 2 through 4 years of age without evidence of infection up to 1 month after Dose 3 based on a data cutoff date of 29 April 2022.

Table 21 presents the specific demographic characteristics in the studied evaluable immunogenicity population.

Table 21. Demographics Characteristics – Immunobridging Subset – Participants 2 Through 4 Years of Age (Study 3) and Participants 16 Through 25 Years of Age (Study 2) – Without Evidence of Infection -Evaluable Immunogenicity Population[101]

	TRADENAME 3 mcg/Dose 2 Through 4 Years of Age (N^a=143) n^b (%)	TRADENAME 30 mcg/Dose 16 Through 25 Years of Age (N^a=170) n^b (%)
Sex		
Male	63 (44.1)	79 (46.5)
Female	80 (55.9)	91 (53.5)

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	TRADENAME 3 mcg/Dose 2 Through 4 Years of Age (N[a]=143) n[b] (%)	TRADENAME 30 mcg/Dose 16 Through 25 Years of Age (N[a]=170) n[b] (%)
Age at Vaccination (years)		
Mean (SD)	2.7 (0.76)	21.2 (2.95)
Median	3.0	2.0
Min, max	(2, 4)	(16, 25)
Race		
White	99 (69.2)	130 (76.5)
Black or African American	8 (5.6)	15 (8.8)
American Indian or Alaska Native	0	3 (1.8)
Asian	16 (11.2)	13 (7.6)
Native Hawaiian or other Pacific Islander	0	1 (0.6)
Other[c]	20 (14.0)	8 (4.7)
Ethnicity		
Hispanic or Latino	16 (11.2)	51 (30.0)
Not Hispanic or Latino	126 (88.1)	119 (70.0)
Not reported	1 (0.7)	0

Note: Participants who had no serological or virological evidence (up to 1 month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at pre-Dose 1 and 1 month after Dose 2, SARS-CoV-2 not detected by NAAT [nasal swab] at pre-Dose 1 and pre-Dose 2, and negative NAAT [nasal swab] at any unscheduled visit up to 1 month after Dose 2 blood collection) and had no medical history of COVID-19 were included in the analysis.

a. N = Number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. Includes multiracial and not reported.

SARS-CoV-2 50% neutralizing antibody titers (NT50) were compared between an immunogenicity subset of Phase 2/3 participants 2 through 4 years of age from Study 3 at 1 month after the 3-dose primary course and a randomly selected subset from Study 2 (Phase 2/3) participants 16 through 25 years of age at 1 month after the 2-dose primary course, using a microneutralization assay against the reference strain (USA_WA1/2020). The primary immunobridging analyses compared the geometric mean titers (using a GMR) and the seroresponse (defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from before Dose 1) rates in the evaluable immunogenicity population of participants without evidence of prior SARS-CoV-2 infection up to 1 month after Dose 3 in participants 2 through 4 years of age and up to 1 month after Dose 2 in participants 16 through 25 years of age. The prespecified immunobridging criteria were met for both the GMR and the seroresponse difference (Table 22 and Table 23, respectively).

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Table 22. SARS-CoV-2 GMTs (NT50) at 1 Month After Vaccination Course – Immunobridging Subset - Participants 2 Through 4 Years of Age (Study 3) 1 Month After Dose 3 and Participants 16 Through 25 Years of Age (Study 2) 1 Month After Dose 2 – Without Evidence of SARS-CoV-2 Infection – Evaluable Immunogenicity Population[102]

	TRADENAME		
	3 mcg/Dose 2 Through 4 Years of Age (1 month After Dose 3) n[a]=143	30 mcg/Dose 16 Through 25 Years of Age (1 Month After Dose 2) n[a]=170	GMR (95%CI) (2 Through 4 Years of Age/16 Through 25 Years of Age)[c,d]
Assay	**GMT[b] (95% CI[b])**	**GMT[b] (95% CI[b])**	
SARS-CoV-2 neutralization assay - NT50 (titer)[e]	1535.2 (1388.2, 1697.8)	1180.0 (1066.6, 1305.4)	1.30 (1.13, 1.50)

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Participants who had no serological or virological evidence [(up to 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3) blood sample collection)] of past SARS-CoV-2 infection [i.e., N-binding antibody [serum] negative at Dose 1, Dose 3 (Study 3) and 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3), SARS-CoV-2 not detected by NAAT [nasal swab] at Dose 1, Dose 2, and Dose 3 (Study 3) study visits, and negative NAAT [nasal swab] at any unscheduled visit up to 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3) blood collection] and had no medical history of COVID-19 were included in the analysis.

a. n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
b. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
c. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titers (2 to 4 years of age minus 16 to 25 years of age) and the corresponding CI (based on the Student t distribution).
d. Immunobridging is declared if the lower bound of the 2-sided 95% CI for the GMR ratio is greater than 0.67 and the point estimate of the GMR is ≥0.8.
e. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

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Table 23. Difference in Percentages of Participants With Seroresponse at 1 Month After Vaccination Course – Immunobridging Subset –Participants 2 Through 4 Years of Age (Study 3) 1 Month After Dose 3 and Participants 16 Through 25 Years of Age (Study 2) 1 Month After Dose 2 Without Evidence of Infection – Evaluable Immunogenicity Population[103]

	TRADENAME		
	3 mcg/Dose 2 Through 4 Years of Age (1 Month After Dose 3) N[a]=141	30 mcg/Dose 16 Through 25 Years of Age (1 Month After Dose 2) N[a]=170	Difference in Seroresponse Rates %[d] (95% CI[e]) (2 Through 4 Years of age Minus 16 Through 25 Years of Age)[f]
Assay	n[b] (%) (95% CI[c])	n[b] (%) (95% CI[c])	
SARS-CoV-2 neutralization assay - NT50 (titer)[g]	141 (100.0) (97.4, 100.0)	168 (98.8) (95.8, 99.9)	1.2 (-1.5, 4.2)

Abbreviations: LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer 50; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result ≥4 × LLOQ is considered a seroresponse.

Note: Participants who had no serological or virological evidence (up to 1 month after Dose 2 [(Study 2) or 1 month after Dose 3 (Study 3) blood sample collection)[of past SARS-CoV-2 infection [i.e., N-binding antibody [serum] negative at pre-Dose 1, pre-Dose 3 (Study 3) and 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3), SARS-CoV-2 not detected by NAAT [nasal swab] at pre-Dose 1, pre-Dose 2, and pre-Dose 3 (Study 3) study visits, and negative NAAT [nasal swab] at any unscheduled visit up to 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3) blood collection] and had no medical history of COVID-19 were included in the analysis.

a. N = Number of participants with valid and determinate assay results both before vaccination and at 1 month after Dose 2. These values are the denominators for the percentage calculations.
b. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.
c. Exact 2-sided CI based on the Clopper and Pearson method.
d. Difference in proportions, expressed as a percentage (2 through 4 years of age minus 16 through 25 years of age).
e. 2-sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
f. Immunobridging is declared if the lower bound of the 2-sided 95% CI for the difference in proportions is greater than -10.0% provided that the immunobridging criteria based on GMR were met.
g. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

Using a non-validated fluorescence focus reduction neutralization test assay against the Omicron variant of SARS-CoV-2 (BA.1), the NT50 GMT at 1 month after Dose 3 among a subset of 34 study participants without evidence of prior SARS-CoV-2 infection (82.5 [2-sided 95% CI: 55.4, 122.9]) was increased compared to the NT50 GMT before Dose 3 (14.0 [2-sided 95% CI: 10.6, 18.5]).

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An additional descriptive immunogenicity analysis was performed for participants 2 through 4 years of age who received a 3-dose course of TRADENAME in Study 3 (Phase 2/3), compared with a subset of participants 18 through 50 years of age in Study C4591017 (Phase 3) who had received a 2-dose primary course followed by a booster dose of TRADENAME 30 mcg. The comparator group (participants 18 through 50 years of age) in this analysis had a similar interval between TRADENAME Dose 2 and Dose 3 (median 13.0 weeks) as the participants 2 to 4 years of age (median 10.6 weeks). Among 34 participants 2 through 4 years of age without evidence of prior SARS-CoV-2 infection who received 3 doses of TRADENAME 3 mcg, neutralizing GMTs were 114.3 at 1-month post-Dose 3. Among 27 participants 18 through 50 years of age without evidence of prior SARS-CoV-2 infection who received 3 doses of TRADENAME 30 mcg, Omicron neutralizing GMTs were 164.2 at 1-month post-Dose 3.

Infants 6 through 23 months of age – after 3 doses[86]
A descriptive efficacy analysis of Study 3 has been performed in participants 6 through 23 months of age. This analysis evaluated confirmed symptomatic COVID-19 cases accrued up to a data cutoff date of 29 April 2022.

Table 24 presents the specific demographic characteristics in participants 6 through 23 months of age who received 3 doses of TRADENAME (3 mcg modRNA) or placebo.

Table 24. Demographics Characteristics – Phase 2/3 – Participants 6 Through 23 Months of Age – Dose 3 All-Available Efficacy Population[104]

	TRADENAME 3 mcg/Dose (N[a]=386) n[b] (%)	**Placebo (N[a]=184) n[b] (%)**
Sex		
Male	189 (49.0)	79 (42.9)
Female	197 (51.0)	105 (57.1)
Age at Vaccination (months)		
Mean (SD)	15.4 (4.92)	15.2 (5.14)
Median	16.0	15.5
Min, max	(6, 23)	(6, 23)
Race		
White	290 (75.1)	136 (73.9)
Black or African American	10 (2.6)	11 (6.0)
American Indian or Alaska Native	1 (0.3)	0
Asian	42 (10.9)	17 (9.2)
Other[c]	43 (11.1)	20 (10.9)
Ethnicity		
Hispanic or Latino	40 (10.4)	13 (7.1)
Not Hispanic or Latino	344 (89.1)	169 (91.8)
Not reported	2 (0.5)	2 (1.1)

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	TRADENAME 3 mcg/Dose (N[a]=386) n[b] (%)	Placebo (N[a]=184) n[b] (%)
Comorbidities[d]		
Yes	17 (4.4)	9 (4.9)
No	369 (95.6)	175 (95.1)

Abbreviation: SD = standard deviation.
a. N = Number of participants in the specified group from the Dose 3 all-available efficacy population. This value is the denominator for the percentage calculations. Dose 3 all-available efficacy population included all randomized participants who received 3 doses of TRADENAME (3 mcg modRNA) or placebo.
b. n = Number of participants with the specified characteristic.
c. Includes multiracial and not reported.
d. Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as participants who had at least 1 of the prespecified comorbidities based on Morbidity and Mortality Weekly Report 69(32);1081-1088.

The descriptive vaccine efficacy results after dose 3 in participants 6 through 23 months of age are presented in Table 25.

Table 25. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 3 – Phase 2/3 – Participants 6 Through 23 Months of Age – Dose 3 All-available Efficacy Population (Blinded Follow-up Period)[105]

	TRADENAME 3 mcg/Dose N[a]=386 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=184 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy (%) (95% CI[e])
First COVID-19 occurrence from 7 days after Dose 3	1 0.030 (277)	2 0.015 (139)	75.5 (-370.1, 99.6)

Abbreviation: VE = vaccine efficacy.
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; inability to eat/poor feeding).
a. N = Number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1,000 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 3 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Two-sided 95% confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.

Additional evaluation of vaccine efficacy for cases confirmed at least 7 days after Dose 2 and before Dose 3 was performed. In the evaluable efficacy population in participants without prior evidence of SARS-CoV-2 infection before or during the vaccination regimen the observed

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vaccine efficacy from at least 7 days after Dose 2 and before Dose 3 was 16.1% (2-sided 95% CI: -24.9%, 43.1%). The vaccine efficacy in participants with or without prior evidence of SARS-CoV-2 infection before or during the vaccination regimen was similar.

Analysis of COVID-19 cases that excluded those involving coinfection with other respiratory pathogens did not meaningfully impact the estimated vaccine efficacy in this population.

One participant in the placebo group, had confirmed COVID-19 which met a single severe case criterion described in the protocol (increased heart rate [172 bpm]). None of the cases accrued met criteria for multisystem inflammatory syndrome in children (MIS-C).

Immunogenicity analyses have been performed in the immunobridging subset of 82 Study 3 participants 6 through 23 months of age without evidence of infection up to 1 month after Dose 3 based on a data cutoff date of 29 April 2022.

Table 26 presents the specific demographic characteristics in the studied evaluable immunogenicity population.

Table 26. Demographics Characteristics – Immunobridging Subset – Participants 6 Through 23 Months of Age (Study 3) and Participants 16 Through 25 Years of Age (Study 2) – Without Evidence of Infection -Evaluable Immunogenicity Population[106]

	TRADENAME 3 mcg/Dose 6 Through 23 Months of Age (N[a]=82) n[b] (%)	**TRADENAME 30 mcg/Dose 16 Through 25 Years of Age (N[a]=170) n[b] (%)**
Sex		
Male	51 (62.2)	79 (46.5)
Female	31 (37.8)	91 (53.5)
Age at Vaccination (years)		
Mean (SD)	15.7 (4.84)	21.2 (2.95)
Median	16.0	2.0
Min, max	(6, 23)	(16, 25)
Race		
White	59 (72.0)	130 (76.5)
Black or African American	1 (1.2)	15 (8.8)
American Indian or Alaska Native	1 (1.2)	3 (1.8)
Asian	11 (13.4)	13 (7.6)
Native Hawaiian or other Pacific Islander	0	1 (0.6)
Other[c]	10 (12.2)	8 (4.7)

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	TRADENAME 3 mcg/Dose 6 Through 23 Months of Age (N[a]=82) n[b] (%)	TRADENAME 30 mcg/Dose 16 Through 25 Years of Age (N[a]=170) n[b] (%)
Ethnicity		
Hispanic or Latino	13 (15.9)	51 (30.0)
Not Hispanic or Latino	69 (84.1)	119 (70.0)

Note: Participants who had no serological or virological evidence (up to 1 month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at pre-Dose 1 and 1 month after Dose 2, SARS-CoV-2 not detected by NAAT [nasal swab] at pre-Dose 1 and pre-Dose 2, and negative NAAT [nasal swab] at any unscheduled visit up to 1 month after Dose 2 blood collection) and had no medical history of COVID-19 were included in the analysis.

a. N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. Includes multiracial and not reported.

SARS-CoV-2 50% neutralizing antibody titers (NT50) 1 month after the vaccination course were compared between an immunogenicity subset of Phase 2/3 participants 6 through 23 months of age from Study 3 and a randomly selected subset from Study 2 (Phase 2/3) participants 16 through 25 years of age, using a microneutralization assay against the reference strain (USA_WA1/2020). The primary immunobridging analyses compared the geometric mean titers (using a GMR) and the seroresponse (defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from before Dose 1) rates in the evaluable immunogenicity population of participants without evidence of prior SARS-CoV-2 infection up to 1 month after Dose 3 in participants 6 through 23 months of age and up to 1 month after Dose 2 in participants 16 through 25 years of age. The prespecified immunobridging criteria were met for both the GMR and the seroresponse difference (Table 27 and Table 28, respectively).

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Table 27. SARS-CoV-2 GMTs (NT50) at 1 Month After Vaccination Course – Immunobridging Subset - Participants 6 Through 23 Months of Age (Study 3) 1 Month After Dose 3 and Participants 16 rough 25 Years of Age (Study 2) 1 Month After Dose 2 – Without Evidence of SARS-CoV-2 – Evaluable Immunogenicity Population[107]

	TRADENAME		
	3 mcg/Dose 6 Through 23 Months of Age (1 Month After Dose 3) n[a]=82	30 mcg/Dose 16 Through 25 Years of Age (1 Month After Dose 2) n[a]=170	GMR (95%CI) (6 Through 23 Months of Age/16 Through 25 Years of Age)[c,d]
Assay	GMT[b] (95% CI[b])	GMT[b] (95% CI[b])	
SARS-CoV-2 neutralization assay - NT50 (titer)[e]	1406.5 (1211.3, 1633.1)	1180.0 (1066.6, 1305.4)	1.19 (1.00, 1.42)

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Participants who had no serological or virological evidence [(up to 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3) blood sample collection)] of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Dose 1, Dose 3 (Study 3) and 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3), SARS-CoV-2 not detected by NAAT [nasal swab] at Dose 1, Dose 2, and Dose 3 (Study 3) study visits, and negative NAAT [nasal swab] at any unscheduled visit up to 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3) blood collection)] and had no medical history of COVID-19 were included in the analysis.

a. n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
b. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
c. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titers (6 through 23 months of age minus 16 through 25 years of age) and the corresponding CI (based on the Student t distribution).
d. Immunobridging is declared if the lower bound of the 2-sided 95% CI for the GMR ratio is greater than 0.67 and the point estimate of the GMR is ≥0.8.
e. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

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Table 28. Difference in Percentages of Participants With Seroresponse at 1 Month After Vaccination Course – Immunobridging Subset – Participants 6 Through 23 Months of Age (Study 3) 1 Month After Dose 3 and Participants 16 Through 25 Years of Age (Study 2) to 1 Month After Dose 2 Without Evidence of Infection – Evaluable Immunogenicity Population[108]

	TRADENAME		
	3 mcg/Dose 6 Through 23 Months of Age (1 Month After Dose 3) N[a]=80	30 mcg/Dose 16 Through 25 Years of Age (1 Month After Dose 2) N[a]=170	Difference in Seroresponse Rates %[d] (95% CI[e]) (6 Through 23 Months of Age Minus 16 Through 25 Years of Age)[f]
Assay	n[b] (%) (95% CI[c])	n[b] (%) (95% CI[c])	
SARS-CoV-2 neutralization assay - NT50 (titer)[g]	80 (100.0) (95.5, 100.0)	168 (98.8) (95.8, 99.9)	1.2 (-3.4, 4.2,)

Abbreviations: LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer 50; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result ≥4 × LLOQ is considered a seroresponse.

Note: Participants who had no serological or virological evidence [(up to 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3) blood sample collection) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at pre-Dose 1, Dose 3 (Study 3) and 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3), SARS-CoV-2 not detected by NAAT [nasal swab] at pre-Dose 1, pre-Dose 2, and pre-Dose 3 (Study 3) study visits, and negative NAAT [nasal swab] at any unscheduled visit up to 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3) blood collection)] and had no medical history of COVID-19 were included in the analysis.

a. N = Number of participants with valid and determinate assay results both before vaccination and at 1 month after Dose 2. These values are the denominators for the percentage calculations.
b. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.
c. Exact 2-sided CI based on the Clopper and Pearson method.
d. Difference in proportions, expressed as a percentage (6 through 23 months of age minus 16 through 25 years of age).
e. 2-sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
f. Immunobridging is declared if the lower bound of the 2-sided 95% CI for the difference in proportions is greater than -10.0% provided that the immunobridging criteria based on GMR were met.
g. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

Using a non-validated fluorescence focus reduction neutralization test assay against the Omicron variant of SARS-CoV-2 (BA.1), the NT50 GMT at 1 month after Dose 3 among a subset of 32 study participants without evidence of prior SARS-CoV-2 infection (127.5 [2-sided 95% CI: 90.2, 180.1]) was increased compared to the NT50 GMT before Dose 3 (16.3 [2-sided 95% CI: 12.8, 20.8]).

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An additional descriptive immunogenicity analysis was performed for participants 6 through 23 months of age who received a 3-dose course of TRADENAME in Study 3 (Phase 2/3), compared with a subset of participants 18 through 50 years of age in Phase 3 Study C4591017 who had received a 2-dose primary course followed by a booster dose of TRADENAME 30 mcg. The comparator group (participants 18 through 50 years of age) in this analysis had a similar interval between TRADENAME Dose 2 and Dose 3 (median 13.0 weeks) as the participants 6 through 23 months of age (median 12.9 weeks). Among 32 participants 6 through 23 months of age without evidence of prior SARS-CoV-2 infection who received 3 doses of TRADENAME 3 mcg, Omicron neutralizing GMTs were 128.8 at 1-month post-Dose 3. Among 27 participants 18 through 50 years of age without evidence of prior SARS-CoV-2 infection who received 3 doses of TRADENAME 30 mcg, Omicron neutralizing GMTs were 164.2 at 1-month post-Dose 3.

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

Effectiveness of a booster dose of TRADENAME was demonstrated by evaluating noninferiority immune responses of SARS-CoV-2 NT50 1 month after a booster dose. In Study 2, an analysis of SARS-CoV-2 NT50 demonstrated non-inferior immune responses 1 month after a booster dose compared to 1 month after Dose 2 in participants at least 18 through 55 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the booster dose, based on prespecified noninferiority criteria for both GMR and difference in seroresponse rates. Seroresponse for a participant was defined as achieving a ≥4-fold rise from baseline (before Dose 1) in NT50 (Table 29 and Table 30).

The SARS-CoV-2 NT50 GMR of 1 month after the booster dose to 1 month after Dose 2 was 3.26 (2-sided 97.5% CI: 2.76, 3.86), which met the noninferiority criteria for GMR (lower bound of the 2-sided 97.5% CI >0.67 and point estimate of the GMR ≥0.8).

A high proportion of participants (99.5%) had seroresponse 1 month after Dose 3 compared with 95.0% 1 month after Dose 2. The difference in proportions of participants with a seroresponse 1 month after the booster dose (Dose 3) and 1 month after Dose 2 (Dose 3 minus Dose 2) was 1.5% (2-sided 97.5% CI: 1.0%, 7.9%), which met the 10% noninferiority criterion (i.e., lower bound of the 2-sided 97.5% CI >-10%).

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Table 29. Summary of Geometric Mean Ratio for 50% Neutralizing Titer – Comparison of 1 Month After Booster Dose to 1 Month After Dose 2 – Participants Without Evidence of Infection up to 1 Month After Booster Dose* – Booster Dose Evaluable Immunogenicity Population±,71,109,110

		TRADENAME Sampling Time Point			
		1 Month After Booster Dose	1 Month After Dose 2	1 Month After Booster Dose - 1 Month After Dose 2	Met Noninferiority Objective[d] (Y/N)
Assay	n[a]	GMT[b] (95% CI[b])	GMT[b] (95% CI[b])	GMR[c] (97.5% CI[c])	
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)[e]	212	2466.0 (2202.6, 2760.8)	755.7 (663.1, 861.2)	3.26 (2.76, 3.86)	Y

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

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

± All eligible participants who had received 2 doses of TRADENAME as initially randomized, with Dose 2 received within the predefined window (within 19 to 42 days after Dose 1), received a booster dose of TRADENAME, had at least 1 valid and determinate immunogenicity result after booster dose from a blood collection within an appropriate window (within 28 to 42 days after the booster dose), and had no other important protocol deviations as determined by the clinician.

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

b. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.

c. GMRs and 2-sided 97.5% CIs were calculated by exponentiating the mean differences in the logarithms of the assay and the corresponding CIs (based on the Student t distribution).

d. Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the GMR is >0.67 and the point estimate of the GMR is ≥0.80.

e. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

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Table 30. Percentage Difference of Participants Achieving Seroresponse – Comparison of 1 Month After Booster Dose to 1 Month After Dose 2 – Phase 3 – Participants Without Evidence of Infection up to 1 Month After Booster Dose* – Booster Dose Evaluable Immunogenicity Population±,71,110,111

		TRADENAME Sampling Time Point		Difference (1 Month After Booster Dose - 1 Month After Dose 2)	Met Noninferiority Objective[f] (Y/N)
		1 Month After Booster Dose	1 Month After Dose 2		
Assay	N[a]	n[b] % (95% CI[c])	n[b] % (95% CI[c])	%[d] (97.5% CI[e])	
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)[g]	200	199 99.5 (97.2, 100.0)	190 95.0 (91.0, 97.6)	4.5 (1.0, 7.9)	Y

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

Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result ≥4 × LLOQ is considered a seroresponse.

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

± All eligible participants who had received 2 doses of TRADENAME as initially randomized, with Dose 2 received within the predefined window (within 19 to 42 days after Dose 1), received a booster dose of TRADENAME, had at least 1 valid and determinate immunogenicity result after booster dose from a blood collection within an appropriate window (within 28 to 42 days after the booster dose), and had no other important protocol deviations as determined by the clinician.

a. N = number of participants with valid and determinate assay results for the specified assay at baseline, 1 month after Dose 2 and 1 month after the booster dose within specified window. These values are the denominators for the percentage calculations.

b. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.

c. Exact 2-sided CI based on the Clopper and Pearson method.

d. Difference in proportions, expressed as a percentage (1 month after booster dose – 1 month after Dose 2).

e. Adjusted Wald 2-sided CI for the difference in proportions, expressed as a percentage.

f. Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the percentage difference is >-10%.

g. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

Relative vaccine efficacy in participants 16 years of age and older – after booster dose[80,112,113]

An interim efficacy analysis of Study 4, a placebo-controlled booster study, was performed in approximately 10,000 participants 16 years of age and older who were recruited from Study 2, evaluated confirmed COVID-19 cases accrued from at least 7 days after booster vaccination up to a data cut-off date of 8 February 2022 (a period when Delta and then Omicron was the predominant variant), which represents a median of 2.8 months (range 0.3 to 7.5 months) post-booster follow-up. Vaccine efficacy of the TRADENAME booster dose after the primary series relative to the placebo booster group who only received the primary series dose was

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assessed. The relative vaccine efficacy information for participants 16 years of age and older is presented in Table 31.

Table 31. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Booster Vaccination – Participants 16 Years of Age and Older Without Evidence of Infection and Participants With or Without Evidence of Infection Prior to 7 Days After Booster Vaccination – Evaluable Efficacy Population[80,114,115]

First COVID-19 occurrence from 7 days after booster dose in participants without evidence of prior SARS-CoV-2 infection*			
	TRADENAME Na=4689 Cases n1b Surveillance Timec (n2d)	**Placebo Na=4664 Cases n1b Surveillance Timec (n2d)**	**Relative Vaccine Efficacye % (95% CIf)**
First COVID-19 occurrence from 7 days after booster vaccination	63 1.098 (4639)	148 0.932 (4601)	63.9 (51.1, 73.5)
First COVID-19 occurrence from 7 days after booster dose in participants with or without evidence of prior SARS-CoV-2 infection			
	TRADENAME Na=4997 Cases n1b Surveillance Timec (n2d)	**Placebo Na=4942 Cases n1b Surveillance Timec (n2d)**	**Relative Vaccine Efficacye % (95% CIf)**
First COVID-19 occurrence from 7 days after booster vaccination	67 1.179 (4903)	150 0.989 (4846)	62.4 (49.5, 72.2)

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 serological or virological evidence (prior to 7 days after receipt of the booster vaccination) 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 Visit 1, and had a negative NAAT [nasal swab] at any unscheduled visit prior to 7 days after booster vaccination) 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 the booster vaccination to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Relative vaccine efficacy of the TRADENAME booster group relative to the placebo group (non-booster).
f. Two-sided confidence interval (CI) for relative vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.

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Immunogenicity in children 5 through <12 years of age – after booster dose[84]

Effectiveness of a booster dose of TRADENAME was based on an assessment of NT50 against the reference strain of SARS-CoV-2 (USA_WA1/2020). Analyses of NT50 1 month after the booster dose compared to before the booster dose (Dose 3) demonstrated a substantial increase in GMTs in individuals 5 through <12 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the booster dose. This analysis is summarized in Table 32.

Table 32. Summary of Geometric Mean Titers – NT50 – Participants Without Evidence of Infection – Phase 2/3 – Immunogenicity Set – 5 Through <12 Years of Age – Evaluable Immunogenicity Population

		TRADENAME 10 mcg/Dose					
		3-Dose Set		2-Dose Set		Total	
Assay	Dose/ Sampling Time Point[a]	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])
SARS-CoV-2 neutralization assay - NT50 (titer)	1 month Prevax	79	20.5 (20.5, 20.5)	67	20.5 (20.5, 20.5)	146	20.5 (20.5, 20.5)
	1 month after Dose 2	29	1659.4 (1385.1, 1988.0)	67	1110.7 (965.3, 1278.1)	96	1253.9 (1116.0, 1408.9)
	3 months Prevax	67	271.0 (229.1, 320.6)	-	-	67	271.0 (229.1, 320.6)
	1 month after Dose 3	67	2720.9 (2280.1, 3247.0)	-	-	67	2720.9 (2280.1, 3247.0)

Abbreviations: CI = confidence interval; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer; Prevax = before vaccination; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Three-dose immunogenicity set included the first 130 participants who received Dose 3 and completed 1-month post–Dose 3 visit prior to March 15, 2022. Among those, 30 had blood sample collection at 1-month post-Dose 2. Two-dose immunogenicity set included an extra 67 participants randomly selected from previous Dose-2 evaluable immunogenicity population and without evidence of infection up to 1-month post–Dose 2 subset used for 2-dose immunobridging analysis.
Note: Participants included in this analysis had no serological or virological evidence of past SARS-CoV-2 infection up to the 1-month post–Dose 2 (for 1-month post–Dose 2 time point) or 1-month post–Dose 3 (for pre–Dose 3 and 1-month post–Dose 3 time point) study blood sample collection. Having no evidence of past SARS-CoV-2 infection up to 1-month post–Dose 2 was defined as having a negative N-binding antibody (serum) result at the Dose 1 and 1-month post–Dose 2 study visits; a negative NAAT (nasal swab) result at the Dose 1 and Dose 2 study visits and any unscheduled visit prior to the 1-month post–Dose 2 blood sample collection; and no medical history of COVID-19. Having no evidence of past SARS-CoV-2 infection up to 1-month post-Dose 3 was defined as having a negative N-binding antibody (serum) result at the Dose 1, 1-month post–Dose 2 (if available), Dose 3, and 1-month post–Dose 3 study visits; a negative NAAT (nasal swab) result at the Dose 1, Dose 2, and Dose 3 study visits and any unscheduled visit prior to the 1-month post–Dose 3 blood sample collection; and no medical history of COVID-19.
a. Protocol-specified timing for blood sample collection.
b. n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.

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c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.

Immunogenicity in children 5 through <12 years of age on the Omicron variant – after booster dose[84]

The neutralizing GMTs against both the Omicron variant and reference strain were substantially increased after booster vaccination compared with after the 2-dose primary series. At 1-month post-Dose 2, the observed neutralizing GMTs for the Omicron variant and reference strain were 27.6 and 323.8, respectively. At 1-month post-Dose 3, the observed neutralizing GMTs for the Omicron variant and reference strain were 614.4 and 1702.8, respectively (see Table 33).

For the Omicron variant, neutralizing titers after booster vaccination (1-month post-Dose 3) increased 22-fold over those after the 2-dose primary series (1-month post-Dose 2). For the reference strain, the increase after the booster relative to the primary series was 5.3-fold.

Table 33. Summary of Geometric Mean Titers – Omicron-Neutralization Subset – Participants Without Evidence of Infection – Phase 2/3 – Immunogenicity Set – 5 Through <12 Years of Age – Evaluable Immunogenicity Population

		TRADENAME 10 mcg/Dose	
		Vaccine Group (as Randomized)	
Assay	Time Point[b]	n[b]	GMT[c] (95% CI[c])
SARS-COV-2 FFRNT- B.1.1.529 strain (Omicron) - NT50 (titer)	1 month after Dose 2	29	27.6 (22.1, 34.5)
	1 month after Dose 3	17	614.4 (410.7, 919.2)
SARS-CoV-2 FFRNT- reference strain - NT50 (titer)	1 month after Dose 2	29	323.8 (267.5, 392.1)
	1 month after Dose 3	17	1702.8 (1282.6, 2260.7)

Abbreviations: CI = confidence interval; FFRNT = fluorescence focus reduction neutralization test; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Participants included in this analysis had no serological or virological evidence of past SARS-CoV-2 infection up to the 1-month post–Dose 2 (for 1-month post–Dose 2 time point) or 1-month post–Dose 3 (for 1-month post–Dose 3 time point) study blood sample collection. Having no evidence of past SARS-CoV-2 infection up to 1-month post–Dose 2 was defined as having a negative N-binding antibody (serum) result at the Dose 1 and 1-month post–Dose 2 study visits; a negative NAAT (nasal swab) result at the Dose 1 and Dose 2 study visits and any unscheduled visit prior to the 1-month post–Dose 2 blood sample collection; and no medical history of COVID-19. Having no evidence of past SARS-CoV-2 infection up to 1-month post–Dose 3 was defined as having a negative N-binding antibody (serum) result at the Dose 1, 1-month post–Dose 2 (if available), Dose 3, and 1-month post–Dose 3 study visits; a negative NAAT (nasal swab) result at the Dose 1, Dose 2, and Dose 3 study visits and any unscheduled visit prior to the 1-month post–Dose 3 blood sample collection; and no medical history of COVID-19.

a. Protocol-specified timing for blood sample collection.

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b. n = Number of participants with valid and determinate assay results for the specified assays at the given dose/sampling time point.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.

5.2. Pharmacokinetic properties

Not applicable.

5.3. Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients[2,3,74,116]

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

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

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

TRADENAME (Do Not Dilute)

Or

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

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TRADENAME (for age 5 years to <12 years)

Or

*[Editorial Guidance for countries: Select this text for the **Tris/Sucrose presentation, 3 micrograms/dose.**]*

TRADENAME (for age 6 months to <5 years)

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

6.2. Incompatibilities

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

6.3. Shelf life

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

TRADENAME (Dilute Before Use)

Unopened vial

12 months at -90 °C to -60 °C.[63,70,83]

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 ºC to -60 ºC; not exceeding the printed expiry date (EXP).[39]

Once removed from the freezer, the unopened vial can be stored for up to 1 month at 2 °C to 8 °C; not exceeding the printed expiry date (EXP). Within the 1-month shelf life at 2 °C to 8 °C, up to 48 hours may be used for transportation.[29,63,117] 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.

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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.

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

TRADENAME (Do Not Dilute)[75]

Unopened vial

12 months when stored at -90 °C to -60 °C.[79,83]

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

Once removed from frozen storage, the unopened vial may be stored refrigerated at 2 °C to 8 °C for a single period of up to 10 weeks; not exceeding the printed expiry date (EXP).[79]

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

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

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

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

Thawed vials can be handled in room light conditions.

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

Opened vial

Chemical and physical in-use stability has been demonstrated for 12 hours at 2 ºC to 30 ºC. From a microbiological point of view, unless the method of opening precludes the risks of microbial contamination, the product should be used immediately after the first puncture. If not used immediately, in-use storage times and conditions are the responsibility of the user.[77]

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

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

Unopened vial

12 months when stored at -90 °C to -60 °C.[79,83]

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

Once removed from frozen storage, the unopened vial may be stored refrigerated at 2 °C to 8 °C for a single period of up to 10 weeks; not exceeding the printed expiry date (EXP).[79]

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

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

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

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

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Thawed vials can be handled in room light conditions.

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

Diluted medicinal product

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

*[Editorial Guidance for countries: Select this text for the **Tris/Sucrose presentation, 3 micrograms/dose**.]*

TRADENAME (for age 6 months to <5 years)[118]

Unopened vial

12 months when stored at -90 °C to -60 °C.

TRADENAME (for age 6 months to <5 years) will be received frozen at -90 °C to -60 °C.[76] Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

Once removed from frozen storage, the unopened vial may be stored refrigerated at 2 °C to 8 °C for a single period of up to 10 weeks; not exceeding the printed expiry date (EXP).

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

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

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

Vaccine may be stored at temperatures between 8 ºC to 30 ºC for up to 24 hours, including any time at these temperatures following dilution.

Thawed vials can be handled in room light conditions.

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

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Diluted medicinal product[119]

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

6.4. Special precautions for storage[2,25,75,101]

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

TRADENAME (Dilute Before Use)

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

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

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

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

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

TRADENAME (Do Not Dilute)

Or

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

TRADENAME (for age 5 years to <12 years)

Or

*[Editorial Guidance for countries: Select this text for the **Tris/Sucrose presentation, 3 micrograms/dose.]***

TRADENAME (for age 6 months to <5 years)

TRADENAME (Do Not Dilute),TRADENAME (for age 5 years to <12 years) and TRADENAME (for age 6 months to <5 years) can be stored in a refrigerator at 2 °C to 8 °C for a single period of up to 10 weeks, not exceeding the original expiry date (EXP). Alternatively, the

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vaccine may be stored in a freezer at -90 °C to -60 °C. The expiry date for storage at -90 °C to -60 °C is printed on the vial and outer carton after "EXP".

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

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

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

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

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

Once thawed, the vaccine cannot be re-frozen.

Thawed vials can be handled in room light conditions.

6.5. Nature and contents of container

Information to be provided by local subsidiary.

6.6. Special precautions for disposal and other handling[2,3,26,29,30,35,63,75,77,78,116,117,118,119]

Handling instructions

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

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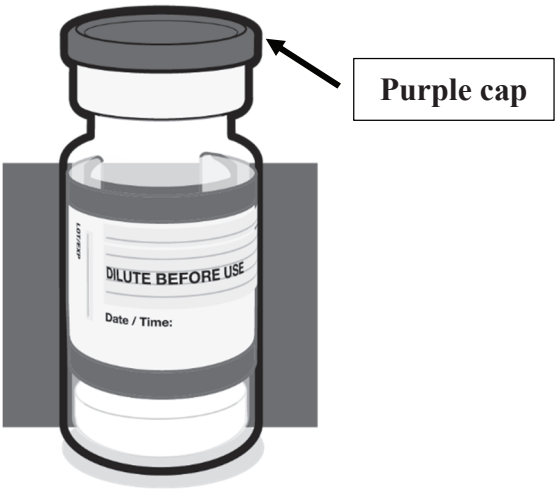
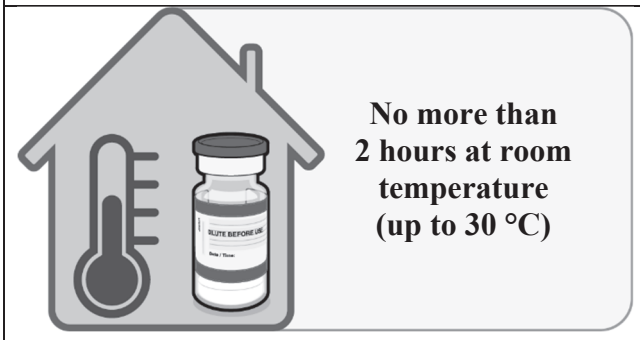
*[Editorial guidance for countries: Select this text for the **PBS/Sucrose presentation, 30 micrograms/dose**.]*

TRADENAME (Dilute Before Use)	
VIAL VERIFICATION	
	Verify that the vial has a purple plastic cap. If the vial has a grey plastic cap, refer to the handling instructions for TRADENAME (Do Not Dilute). If the vial has an orange plastic cap, refer to the handling instructions for TRADENAME (for ages 5 years to <12 years). If the vial has a maroon plastic cap, refer to the handling instructions for TRADENAME (for age 6 months to <5 years).
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; not exceeding the printed expiry date (EXP). Within the 1-month shelf life at 2 °C to 8 °C, up to 48 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.

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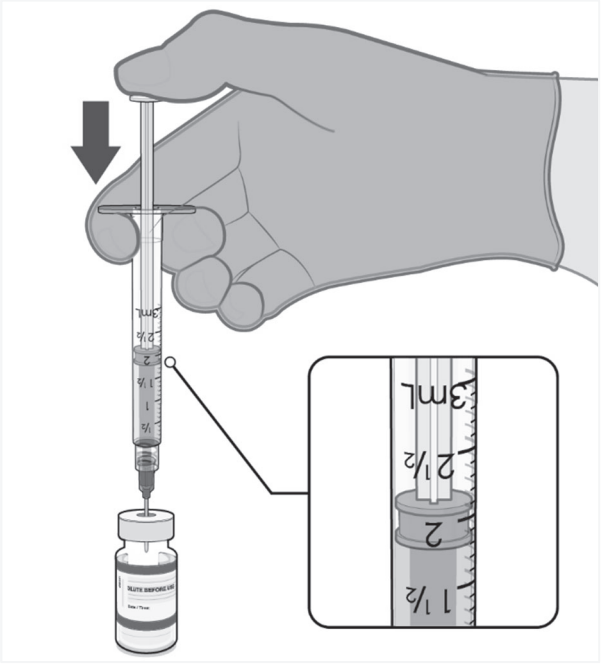
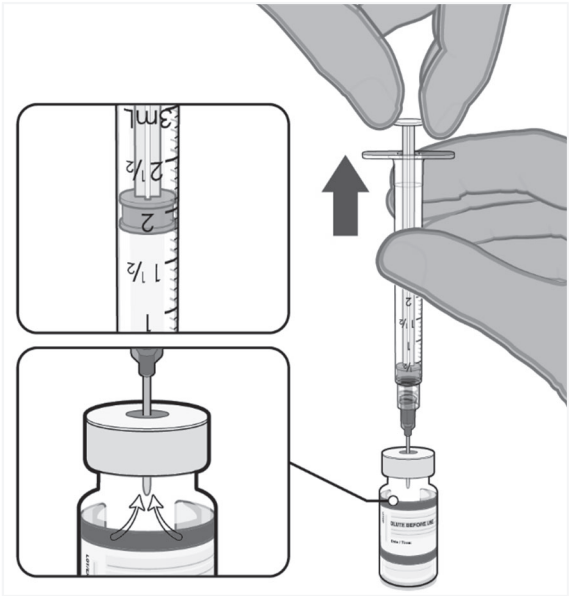
TRADENAME (Dilute Before Use)	
DILUTION	
 **1.8 mL of 0.9% sodium chloride injection**	• The thawed vaccine must be diluted in its original vial with 1.8 mL sodium chloride 9 mg/mL (0.9%) solution for injection, using a 21 gauge or narrower needle and aseptic techniques.
 **Pull back plunger to 1.8 mL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

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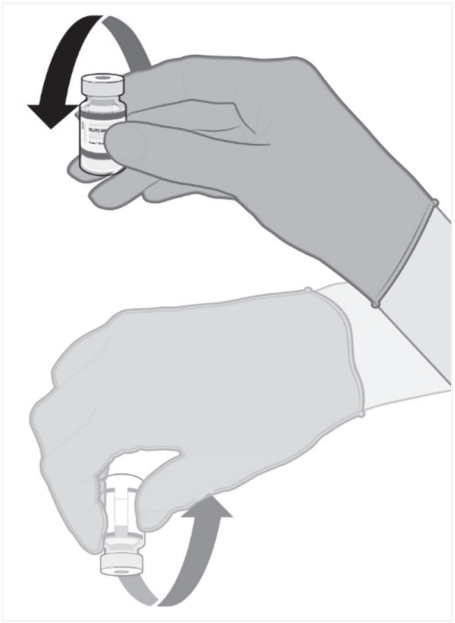
TRADENAME (Dilute Before Use)	
 **Gently × 10**	• Gently invert the diluted dispersion 10 times. Do not shake. • The diluted vaccine should present as an off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discoloration are present.
 **Record appropriate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

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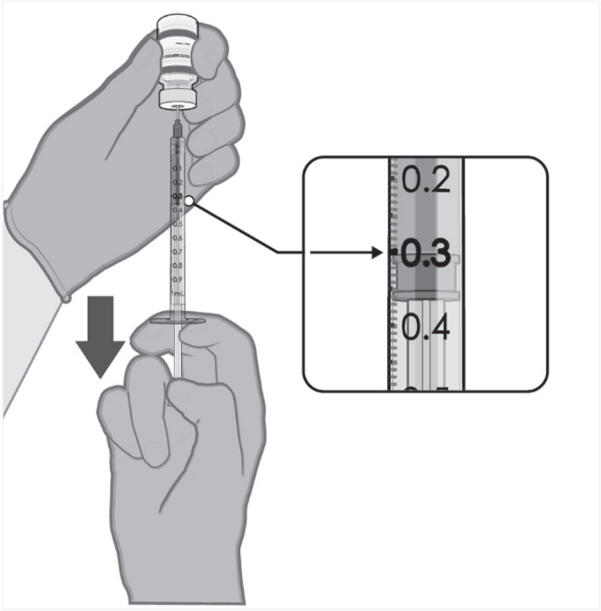
TRADENAME (Dilute Before Use)	
PREPARATION OF INDIVIDUAL 0.3 mL DOSES OF TRADENAME	
 **0.3 mL diluted vaccine**	• After dilution, the vial contains 2.25 mL from which 6 doses of 0.3 mL can be extracted. • Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab. • Withdraw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

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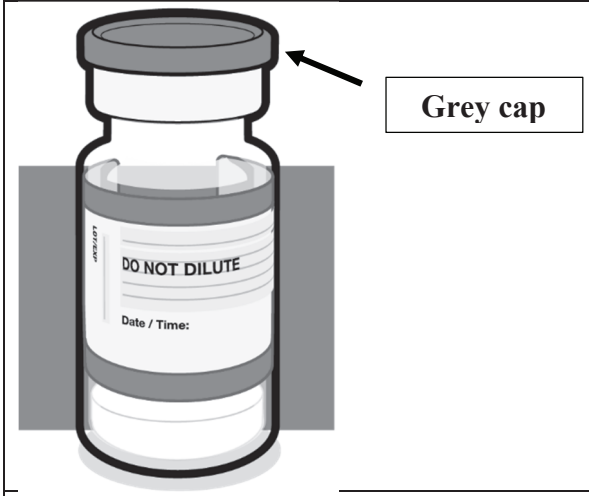
*[Editorial guidance for countries: Select this text for the **Tris/Sucrose presentation, 30 micrograms/dose**.]*

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

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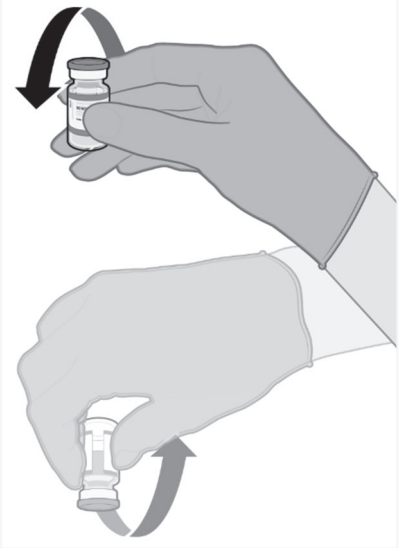
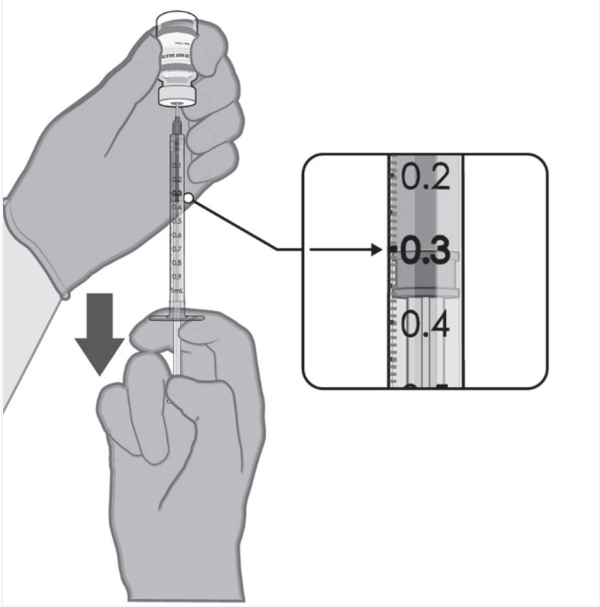
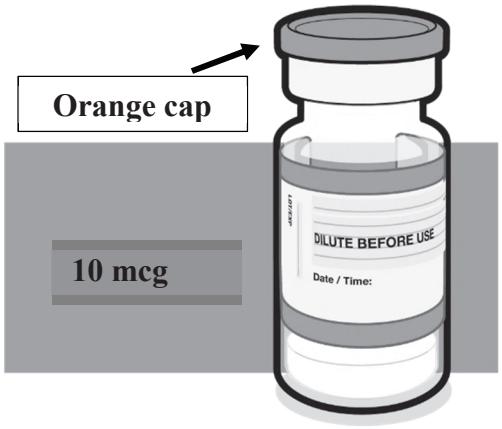
TRADENAME (Do Not Dilute)	
 **Gently × 10**	• Gently mix by inverting vials 10 times prior to use. Do not shake. • Prior to mixing, the thawed dispersion may contain white to off-white opaque amorphous particles. • After mixing, the vaccine should present as a white to off-white dispersion with no particulates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

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

TRADENAME (for age 5 years to <12 years)	
VIAL VERIFICATION	
	• Verify that the vial has an orange plastic cap. If the vial has a purple plastic cap, refer to the handling instructions for TRADENAME (Dilute Before Use). If the vial has a grey plastic cap, refer to the handling instructions for TRADENAME (Do Not Dilute). If the vial has a maroon plastic cap, refer to the handling instructions for TRADENAME (for age 6 months to <5 years).
HANDLING PRIOR TO USE	
	• If the multidose vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 10 vial pack may take 4 hours to thaw. Ensure vials are completely thawed prior to use. • Unopened vials can be stored for up to 10 weeks at 2 °C to 8 °C; not exceeding the printed expiry date (EXP). • Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C for immediate use.

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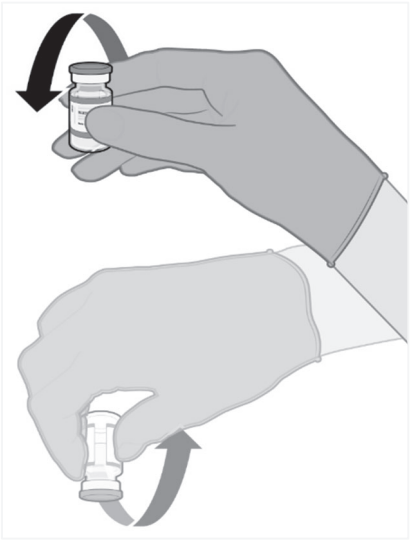
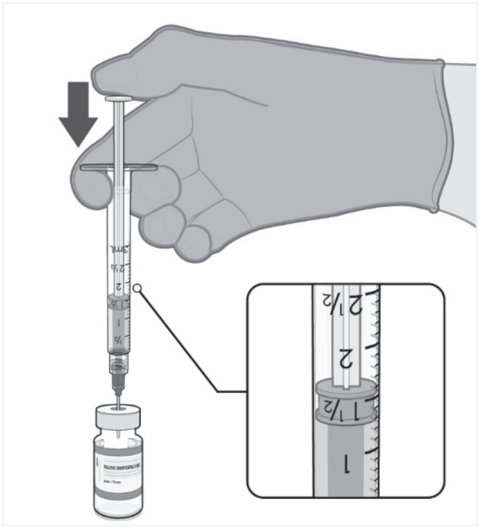
TRADENAME (for age 5 years to <12 years)	
MIXING PRIOR TO DILUTION	
 **Gently × 10**	• Allow the thawed vial to come to room temperature and gently invert it 10 times prior to dilution. Do not shake. • Prior to dilution, the thawed dispersion may contain white to off-white opaque amorphous particles.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

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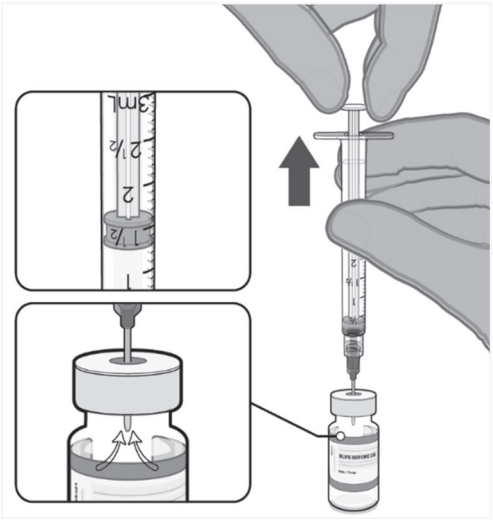
TRADENAME (for age 5 years to <12 years)	
 **Pull back plunger to 1.3 mL to remove air from vial.**	• Equalize vial pressure before removing the needle from the vial stopper by withdrawing 1.3 mL air into the empty diluent syringe.
 **Gently × 10**	• Gently invert the diluted dispersion 10 times. Do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

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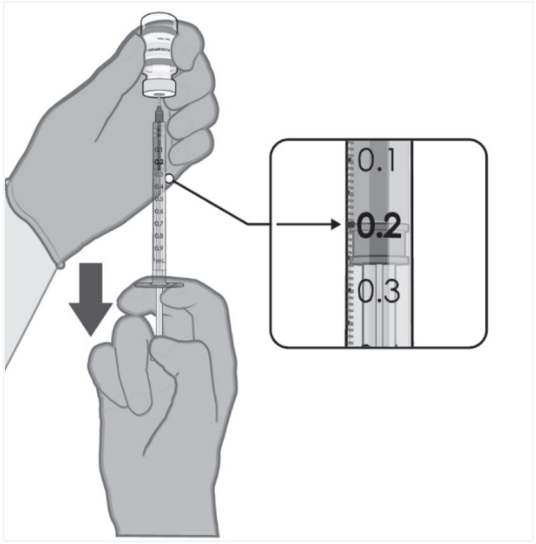
TRADENAME (for age 5 years to <12 years)	
 **Record appropriate date and time.** **Use within 12 hours after dilution.**	• The diluted vials should be marked with the appropriate date and time. • After dilution, store at 2 ºC to 30 ºC and use within 12 hours. • Do not freeze or shake the diluted dispersion.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

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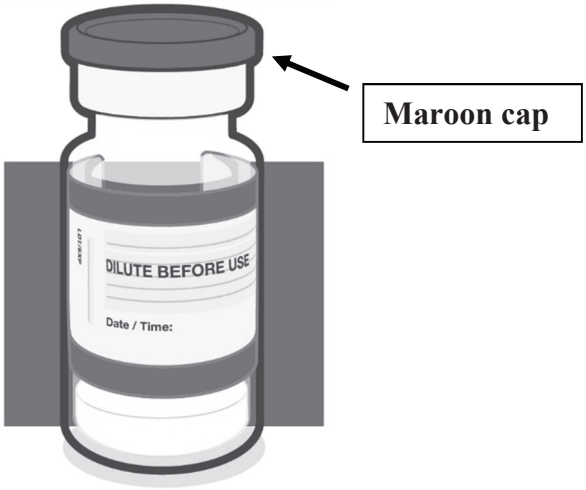
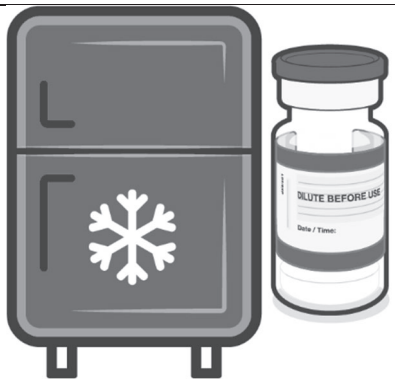
*[Editorial guidance for countries: Select this text for the **Tris/Sucrose presentation, 3 micrograms/dose**.]*

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

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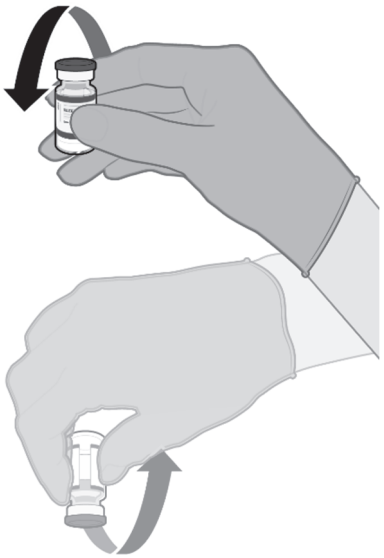
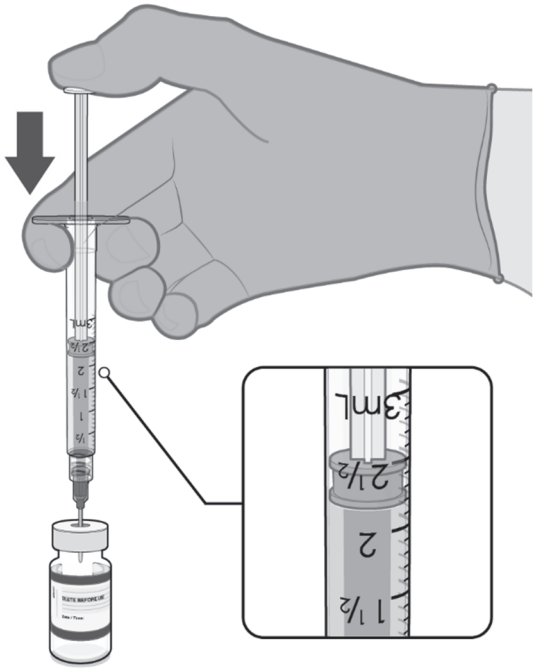
TRADENAME (for age 6 months to <5 years)	
MIXING PRIOR TO DILUTION	
 **Gently × 10**	• Allow the thawed vial to come to room temperature and gently invert it 10 times prior to dilution. Do not shake. • Prior to dilution, the thawed dispersion may contain white to off-white opaque amorphous particles.
DILUTION	
 **2.2 mL of 0.9% sodium chloride**	• The thawed vaccine must be diluted in its original vial with 2.2 mL sodium chloride 9 mg/mL (0.9%) solution for injection, using a 21 gauge or narrower needle and aseptic techniques.

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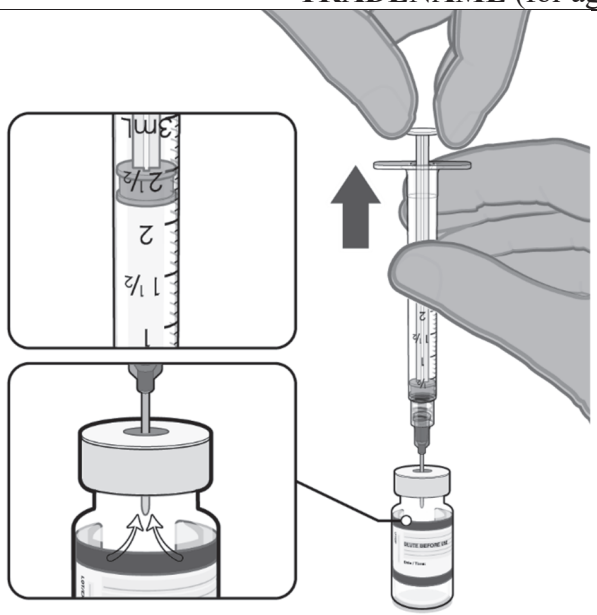
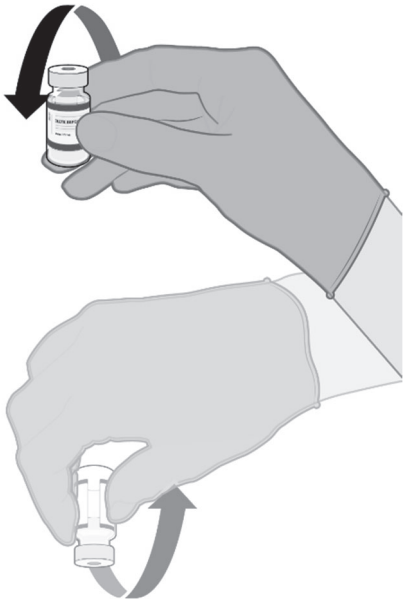
TRADENAME (for age 6 months to <5 years)	
 **Pull back plunger to 2.2 mL to remove air from vial.**	• Equalize vial pressure before removing the needle from the vial stopper by withdrawing 2.2 mL air into the empty diluent syringe.
 **Gently × 10**	• Gently invert the diluted dispersion 10 times. Do not shake. • The diluted vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discoloration are present.

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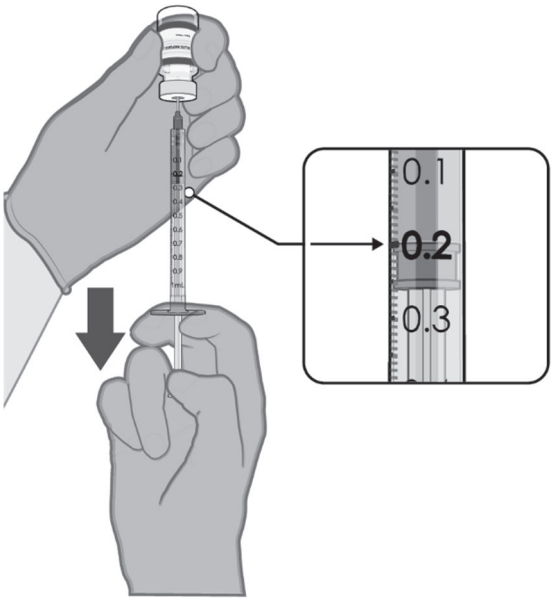
TRADENAME (for age 6 months to <5 years)	
 **Record appropriate date and time.** **Use within 12 hours after dilution.**	• The diluted vials should be marked with the appropriate date and time. • After dilution, store at 2 ºC to 30 ºC and use within 12 hours. • Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.
PREPARATION OF INDIVIDUAL 0.2 mL DOSES OF TRADENAME	
 **0.2 mL diluted vaccine**	• Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab. • Withdraw 0.2 mL of TRADENAME for individuals 6 months through <5 years of age. Low dead-volume syringes and/or needles should be used in order to extract 10 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microliters. If standard syringes and needles are used, there may not be sufficient volume to extract ten doses from a single vial. • Each dose must contain 0.2 mL of vaccine. • If the amount of vaccine remaining in the vial cannot provide a full dose of 0.2 mL, discard the vial and any excess volume. • Discard any unused vaccine within 12 hours after dilution.

Disposal

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

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7. REFERENCES

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

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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

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41. Module 2.7.4 Summary of Clinical Safety, MAA Type II Variation (12-15 Years) Table 6: Demographic Characteristics – Subjects 12 Through 15 and 16 Through 25 Years of Age – Safety Population
42. Table: Follow-up Time After Dose 2 – Subjects 12 Through 15 Years of Age – Safety Population
43. Table: Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population
44. Table: Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population
45. Table: Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 Through 1 Month After Dose 2, by System Organ Class and Preferred Term – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population
46. Table: Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-up Period – Subjects 12 Through 15 Years of Age and Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
47. Table: Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-up Period – Subjects 12 Through 15 Years of Age and With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
48. Table: Summary of Geometric Mean Ratio – NT50 – Comparison of Subjects 12 Through 15 Years of Age to Subjects 16 Through 25 Years of Age (Immunogenicity Subset) – Subjects Without Evidence of Infection up to 1 Month After Dose 2 – Dose 2 Evaluable Immunogenicity Population
49. Module 2.7.4 Summary of Clinical Safety, COVID-19 Vaccine – MAA Type II Variation (12-15 Years) April 2021
50. Interim Report – 6 Month Update: A Phase 1/2/3, Placebo-Controlled, Randomized, Observer-Blind, Dose-Finding Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of SARS-COV-2 RNA Vaccine Candidates Against COVID-19 in Healthy Individuals [hereafter Interim Report – 6 Month Update] (13 March 2021), Supplemental Table 14.198 Demographic Characteristics, by Age Groups – Phase 2/3 Subjects ≥16 Years of Age – Safety Population
51. Interim Report – 6 Month Update (13 March 2021), Supplemental table 14.84 – Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2 – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 HIV Positive Subjects ≥16 Years of Age – Safety Population
52. Final Analysis Interim Report: A Phase 1/2/3, Placebo-Controlled, Randomized, Observer-Blind, Dose-Finding Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of SARS-COV-2 RNA Vaccine Candidates Against COVID-19 in Healthy

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Individuals (04 November 2020), Section 10.3.3 Phase 2/3, Table 8 Vaccine Administration Timing – ~38000 Subjects for Phase 2/3 Analysis – All Randomized Subjects

53. Interim Report – 6 Month Update (13 March 2021), Table 19. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Subgroup – Blinded Placebo-Controlled Follow-up Period – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
54. Interim Report – 6 Month Update (13 March 2021), Supplemental Table 14.59. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Subgroup– Blinded Placebo-Controlled Follow-up Period–Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
55. Interim Report – 6 Month Update (13 March 2021), Table 20. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – Blinded Placebo-Controlled Follow-up Period – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
56. Interim Report – 6 Month Update (13 March 2021), Table 21. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – Blinded Placebo-Controlled Follow-up Period – Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
57. Interim Report – 6 Month Update (13 March 2021), Table 25. Vaccine Efficacy – First Severe COVID-19 Occurrence From 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-up Period – Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
58. Interim Report – 6 Month Update (13 March 2021), Table 26. Vaccine Efficacy – First Severe COVID-19 Occurrence After Dose 1 – Blinded Placebo-Controlled Follow-up Period – Dose 1 All-Available Efficacy Population
59. Interim Report – 6 Month Update (13 March 2021), Supplemental Table 14.61. Vaccine Efficacy – First Severe COVID-19 Occurrence Based on CDC-Definition After Dose 1 – Blinded Placebo-Controlled Follow-up Period – Dose 1 All-Available Efficacy Population
60. Interim Report – 6 Month Update (13 March 2021), Table 28. Vaccine Efficacy – First Severe COVID-19 Occurrence Based on CDC-Definition From 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-up Period – Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
61. EUA Amendment for Pfizer-BioNTech COVID-19 Vaccine, 6-Month Follow-Up Data from Participants 16 Years of Age and Older (13 March 2021), Section 6.2.1.2.1.2 Efficacy
62. Interim Report – 6 Month Update (13 March 2021), Table 4. Analysis Populations
63. Module 3.2.P.8.1 Stability Summary and Conclusion, August 2021
64. Adverse Drug Reaction Frequency Justification Document, COVID-19 Vaccine (BNT162B2), July 2022
65. Interim Report – 6 Month Update (13 March 2021), Supplemental Table 14.72 – Local Reactions, by Maximum Severity, Within 7 Days After Each Dose (Reactogenicity Subset)

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

66. Interim Report – 6 Month Update (13 March 2021), Supplemental Table 14.79 – Systemic Events, by Maximum Severity, Within 7 Days After Each Dose (Reactogenicity Subset) – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 HIV-Positive Subjects ≥16 Years of Age – Safety Population
67. 2.5 Clinical Overview to Support Inclusion of Vaccine Stress-Related Reactions in Section 4.4 of the Core Data Sheet, May 2021
68. EUA Amendment for Pfizer-BioNTech COVID-19 Vaccine, 6-Month Follow-Up Data from Participants 16 Years of Age and Older (13 March 2021), Section 6.2.2.1.1 Study Populations – BNT162-01 Phase 1 Participants
69. 2.5 Clinical Overview to Support Inclusion of Myocarditis & Pericarditis in Section 4.4 (Special Warnings and Precautions for use) of the Core Data Sheet, July 2021
70. Module 3.2.P.8.3 Stability Data, August 2021
71. Interim Report – BNT162b2 Booster (Dose 3): A Phase 1/2/3, Placebo Controlled, Randomized, Observer-Blind, Dose-Finding Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of SARS-CoV-2 RNA Vaccine Candidates Against COVID-19 in Healthy Individuals
72. Module 3.2.P.2.2 Drug Product – Tris-Sucrose, September 2021
73. Interim Report – Children 5 to <12 Years of Age: A Phase 1, Open-Label Dose-Finding Study to Evaluate Safety, Tolerability, and Immunogenicity and Phase 2/3 Placebo-Controlled, Observer-Blinded Safety, Tolerability, and Immunogenicity Study of a SARS-CoV-2 RNA Vaccine Candidate against COVID-19 in Healthy Children and Young Adults
74. Module 3.2.P.1 Description and Composition of the Drug Product – Tris-Sucrose, September 2021
75. Module 3.2.P.8.1 Stability Summary and Conclusion – Tris-Sucrose, September 2021
76. Module 3.2.P.3.5 Shipping Validation – Tris-Sucrose, September 2021
77. Module 3.2.P.2.6 Compatibility – Tris-Sucrose, September 2021
78. Module 3.2.P.2.3 Manufacturing Process Development – Process Development and Characterization – Tris/Sucrose, September 2021
79. Module 3.2.P.8.1 Stability Summary and Conclusions – Tris-Sucrose, November 2021
80. 2.5 Clinical Overview for Adult Booster Efficacy MAA – Study C4591031, November 2021
81. Interim Clinical Study Report, Protocol C4591001 – Interim Report – Adolescent 6-Month Update: A Phase 1/2/3, Placebo-Controlled, Randomized, Observer-Blind, Dose-Finding Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of SARS-CoV-2 mRNA Vaccine Candidates Against COVID-19 in Healthy Individuals
82. Clinical Information Amendment – COVID-19 Vaccine C4591007 (5 to <12 Years) Efficacy Data in Phase 2/3 Study C4591007, October 2021

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83. Module 3.2.P.8.3 Stability Data, August 2021
84. 2.5 Clinical Overview – Pediatric (5-12 Years) Booster MAA Extension – April 2022
85. Module 3.2.P.2.2 Drug Product – Tris-Sucrose, May 2022
86. 2.5 Clinical Overview – Pediatric (6m-5y) Three-Dose Series MAA Extension - June 2022
87. 2.5 Clinical Overview – BNT162b2 30 mcg Adult Booster (Dose 3) sBLA_MAA – May 2022 - 2.5.1.2.4 Proposed Indication
88. 2.5 Clinical Overview – Pediatric (6m-5y) Three-Dose Series MAA Extension - June 2022 - 2.5.1.2.3.2.2 Phase 1/2/3 Study C4591007
89. 2.5 Clinical Overview – To Support Inclusion of Myocarditis and Pericarditis as Adverse Drug Reactions in Section 4.8 of the Core Data Sheet – July 2022
90. 2.5 Clinical Overview – Pediatric (6m-5y) Three-Dose Series MAA Extension - June 2022 – Table 41. Disposition of All Randomized Participants Prior to Unblinding – Phase 2/3 – 2 to <5 Years of Age, Table 40. Follow-Up Time After Dose 2 or Dose 3 – Phase 2/3 – 2 to <5 Years of Age – Safety Population
91. Module 5 Table: Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Phase 2/3 – Blinded Placebo-Controlled Follow-Up Period – 2 to <5 Years of Age – Safety Population
92. Module 5 Table: Systemic Events, by Maximum Severity, Within 7 days After Each Dose – Phase 2/3 – Blinded Placebo-Controlled Follow-Up Period – 2 to <5 Years of Age – Safety Population
93. 2.5 Clinical Overview – Pediatric (6m-5y) Three-Dose Series MAA Extension - June 2022 - Table 50. Disposition of All Randomized Participants Prior to Unblinding – Phase 2/3 – 6 Months to <2 Years of Age
94. Module 5 Table: Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Phase 2/3 – Blinded Placebo-Controlled Follow-Up Period – 6 Months to <2 Years of Age – Safety Population
95. Module 5 Table: Systemic Events, by Maximum Severity, Within 7 days After Each Dose – Phase 2/3 – Blinded Placebo-Controlled Follow-Up Period – 6 Months to <2 Years of Age – Safety Population
96. Interim Clinical Study Report – C4591001 – 19 May 2022 - Table 12. Follow-up Time After Booster Dose – Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 μg)
97. 2.5 Clinical Overview – BNT162b2 30 mcg Adult Booster (Dose 3)_sBLA_MAA – May 2022 - 2.5.4.4.2.1.2 Duration of Follow-Up – C4591031 – 6 Months Post-Dose 3
98. Interim Full Clinical Study Report – C4591031 Substudy A - 6 Month Analysis – 07 June 2022 – Table 10. Follow-Up Time After Booster Vaccination – Safety Population
99. 2.5 Clinical Overview – Pediatric (6m-5y) Three-Dose Series MAA Extension - June 2022 - Table 28. Demographic Characteristics – Phase 2/3 – 2 to <5 Years of Age – Dose 3 All-Available Efficacy Population

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100. 2.5 Clinical Overview – Pediatric (6m-5y) Three-Dose Series MAA Extension - June 2022 - Table 29. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 3 – Blinded Follow-Up Period – Phase 2/3 – 2 to <5 Years of Age – Dose 3 All-Available Efficacy Population
101. 2.5 Clinical Overview – Pediatric (6m-5y) Three-Dose Series MAA Extension - June 2022 – Table 7. Demographic Characteristics – Immunobridging Subset – Participants Without Evidence of Infection – Study C4591007 Phase 2/3 2 to <5 Years of Age and Study C4591001 Phase 2/3 16 Through 25 Years of Age – Evaluable Immunogenicity Population
102. 2.5 Clinical Overview – Pediatric (6m-5y) Three-Dose Series MAA Extension - June 2022 - Table 8. Summary of Geometric Mean Ratios – NT50 – Participants Without Evidence of Infection – Immunobridging Subset – Study C4591007 Phase 2/3 2 to <5 Years of Age (1 Month After Dose 3) and Study C4591001 Phase 2/3 16 Through 25 Years of Age (1 Month After Dose 2) – Evaluable Immunogenicity Population
103. 2.5 Clinical Overview – Pediatric (6m-5y) Three-Dose Series MAA Extension - June 2022 - Table 9. Difference in Percentages of Participants With Seroresponse – Participants Without Evidence of Infection – Immunobridging Subset – Comparison of Study C4591007 Phase 2/3 2 to <5 Years of Age (1 Month After Dose 3) and Study C4591001 Phase 2/3 16 Through 25 Years of Age (1 Month After Dose 2) – Evaluable Immunogenicity Population
104. 2.5 Clinical Overview – Pediatric (6m-5y) Three-Dose Series MAA Extension - June 2022 - Table 34. Demographic Characteristics – Phase 2/3 – 6 Months to <2 Years of Age – Dose 3 All-Available Efficacy Population
105. 2.5 Clinical Overview – Pediatric (6m-5y) Three-Dose Series MAA Extension - June 2022 - Table 35. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 3 – Blinded Follow-Up Period – Phase 2/3 – 6 Months to <2 Years of Age – Dose 3 All-Available Efficacy Population
106. 2.5 Clinical Overview – Pediatric (6m-5y) Three-Dose Series MAA Extension - June 2022 – Table 17. Demographic Characteristics – Immunobridging Subset – Participants Without Evidence of Infection – Study C4591007 Phase 2/3 6 Months to <2 Years of Age and Study C4591001 Phase 2/3 16 Through 25 Years of Age – Evaluable Immunogenicity Population
107. 2.5 Clinical Overview – Pediatric (6m-5y) Three-Dose Series MAA Extension - June 2022 – Table 18. Summary of Geometric Mean Ratios – NT50 – Participants Without Evidence of Infection – Immunobridging Subset – Study C4591007 Phase 2/3 6 Months to <2 Years of Age (1 Month After Dose 3) and Study C4591001 Phase 2/3 16 Through 25 Years of Age (1 Month After Dose 2) – Evaluable Immunogenicity Population
108. 2.5 Clinical Overview – Pediatric (6m-5y) Three-Dose Series MAA Extension - June 2022 – Table 19. Difference in Percentages of Participants With Seroresponse – Participants Without Evidence of Infection – Immunobridging Subset – Comparison of Study C4591007 Phase 2/3 6 Months to <2 Years of Age (1 Month After Dose 3) and Study C4591001 Phase 2/3 16 Through 25 Years of Age (1 Month After Dose 2) – Evaluable Immunogenicity Population
109. Module 5.3.5.1. Table: Geometric Mean Ratio – Comparison of 1 Month After Booster Dose to 1 Month After Dose 2 – Phase 3 – BNT162b2 – Experienced Subjects Without

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Evidence of Infection up to 1 Month After Booster Dose Who Were Rerandomized to Receive 1 Booster Dose (30 ug) – Dose 3 Booster Evaluable Immunogenicity Population

110. Interim Clinical Study Report – C4591001 – 19 May 2022 – Table 4 Analysis Populations
111. Module 5.3.5.1. Table: Percentage Difference of Subjects Achieving Seroresponse – Comparison of 1 Month After Booster Dose to 1 Month After Dose 2 – Phase 3 – BNT162b2 – Experienced Subjects Without Evidence of Infection up to 1 Month After Booster Dose Who Were Rerandomized to Receive 1 Booster Dose (30 ug) – Dose 3 Booster Evaluable Immunogenicity Population
112. 2.5 Clinical Overview – BNT162b2 30 mcg Adult Booster (Dose 3) sBLA_MAA – May 2022 – 2.5.4.4.2.5 Efficacy Conclusions – C4591031 – 6 Months Post-Dose 3
113. 2.5 Clinical Overview – BNT162b2 30 mcg Adult Booster (Dose 3) sBLA_MAA – May 2022 – 2.5.4.4.2.1.2 Duration of Follow-Up - C4591031 - 6 Month Post-Dose 3, Table 14. Follow-Up Time After Booster Vaccination – Participants Without Evidence of Infection Prior to 7 Days After Booster Vaccination – Evaluable Efficacy Population
114. 2.5 Clinical Overview – BNT162b2 30 mcg Adult Booster (Dose 3) sBLA_MAA – May 2022 – 2.5.4.4.2.2 Confirmed COVID-19 Cases – C4591031 – 6 Months Post-Dose 3, Table 16. Vaccine Efficacy - First COVID-19 Occurrence From 7 Days After Booster Vaccination – Blinded Follow-Up Period – Participants Without Evidence of Infection Prior to 7 Days After Booster Vaccination – Evaluable Efficacy Population
115. 2.5 Clinical Overview – BNT162b2 30 mcg Adult Booster (Dose 3) sBLA_MAA – May 2022 – 2.5.4.4.2.2 Confirmed COVID-19 Cases – C4591031 – 6 Months Post-Dose 3, Table 17. Vaccine Efficacy - First COVID-19 Occurrence From 7 Days After Booster Vaccination – Blinded Follow-Up Period – Participants With or Without Evidence of Infection Prior to 7 Days After Booster Vaccination – Evaluable Efficacy Population
116. Module 3.2.P.1 Description and Composition of the Drug Product – Tris-Sucrose – May 2022
117. Module 3.2.P.3.5 Process Validation and/or Evaluation – Shipping Validation – June 2022
118. Module 3.2.P.8.1 Stability Summary and Conclusion – Tris-Sucrose – May 2022
119. Module 3.2.P.2.6 Compatibility – Tris-Sucrose – May 2022

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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)

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)[64]

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

a. Source: Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2, by System Organ Class and Preferred Term – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 Subjects ≥16 Years of Age – Safety Population (Study C4591001, Cut-off 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 (Study C4591001, Cut-off 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 (Study C4591001, Cut-off date: 13March2021).
d. These adverse reactions were identified in the post-authorization period.
e. Due to the cross-over design of clinical trials, the actual incidence of myocarditis and pericarditis cannot be reliably estimated however, based on published literature presented in the Clinical Overview, the CIOMS frequency category for myocarditis and pericarditis is "very rare."[89]

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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)[64]

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]	
Cardiac disorders	Myocarditis[d]	N/A[f]
	Pericarditis[d]	N/A[f]
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 (Study C4591001, Cut-off 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 (Study C4591001, Cut-off 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 (Study C4591001, Cut-off 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: angioedema, pruritus, malaise, lethargy, asthenia, decreased appetite, hyperhidrosis, and night sweats.
f. Due to the cross-over design of clinical trials, the actual incidence of myocarditis and pericarditis cannot be reliably estimated however, based on published literature presented in the Clinical Overview, the CIOMS frequency category for myocarditis and pericarditis is "very rare."[89]

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Table A-3. Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency within each System Organ Class: Individuals 5 Through <12 Years of Age (06 September 2021 Data Cut-off Date)[64]

System Organ Class	ADR Term	Frequency n/N (%)
Blood and lymphatic system disorders	Lymphadenopathy	13/1518 (0.9%)[a]
Immune system disorders	Anaphylaxis[d]	Not known
	Hypersensitivity reactions	
	Rash[d]	5/1518 (0.3%)[a]
	Urticaria[d]	3/1518 (0.2%)[a]
	Pruritus[d]	1/1518 (0.1%)[a]
	Angioedema[d,e]	
Metabolism and nutrition disorders	Decreased appetite	1/1518 (0.1%)[a]
Nervous system disorders	Headache	579/1517 (38.2%)[b]
	Lethargy[e]	
Cardiac disorders	Myocarditis[d,e]	N/A[f]
	Pericarditis[d,e]	N/A[f]
Gastrointestinal disorders	Diarrhea[d]	146/1517 (9.6%)[b]
	Vomiting[d]	60/1517 (4.0%)[b]
	Nausea	6/1518 (0.4%)[a]
Skin and subcutaneous tissue disorders	Hyperhidrosis[e]	
	Night sweats[e]	
Musculoskeletal and connective tissue disorders	Myalgia (muscle pain)	266/1517 (17.5%)[b]
	Arthralgia (joint pain) (new)	115/1517 (7.6%)[b]
	Pain in extremity (arm)[d]	3/1518 (0.2%)[a]
General disorders and administration site conditions	Injection site pain	1279/1517 (84.3%)[c]
	Fatigue	785/1517 (51.7%)[b]
	Injection site redness	401/1517 (26.4%)[c]
	Injection site swelling	309/1517 (20.4%)[c]
	Chills	188/1517 (12.4%)[b]
	Pyrexia	126/1517 (8.3%)[b]
	Malaise	2/1518 (0.1%)[a]
	Asthenia[e]	

a. Source: Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2, by System Organ Class and Preferred Term – Phase 2/3 – 5 to <12 Years of Age – Safety Population (Study C4591007, Cut-off date: 06Sep2021).
b. Source: Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Phase 2/3 – 5 to <12 Years of Age – Safety Population (Study C4591007, Cut-off date: 06Sep2021).
c. Source = Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Phase 2/3 – 5 to <12 Years of Age – Safety Population (Study C4591007, Cut-off date: 06Sep2021).
d. These adverse reactions were identified in the post-authorization period.
e. At the time of the data-lock, the following reactions were not reported in participants 5 through <12 years of age in Study C4591007: **Error! Reference source not found.**angioedema, lethargy, myocarditis, pericarditis, asthenia, hyperhidrosis, and night sweats.
f. Due to the cross-over design of clinical trials, the actual incidence of myocarditis and pericarditis cannot be reliably estimated however, based on published literature presented in the Clinical Overview, the CIOMS frequency category for myocarditis and pericarditis is "very rare."[89]

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Table A-4. Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency Within Each System Organ Class: Individuals 2 to <5 Years of Age (29 April 2022 Data Cut-off Date)[64]

System Organ Class	ADR Term	Frequency n/N (%)
Blood and lymphatic system disorders	Lymphadenopathy	1/1835 (0.1%)[a]
Immune system disorders	Anaphylaxis[d]	Not known
	Hypersensitivity reactions	
	Rash[d,e]	6/1835 (0.3%)[a]
	Urticaria[d]	6/1835 (0.3%)[a]
	Pruritis[d,f]	
	Angioedema[d,f]	
Metabolism and nutrition disorders	Decreased appetite	1/1835 (0.1%)[a]
Nervous system disorders	Headache	159/1826 (8.7%)[b]
	Lethargy[f]	
Cardiac disorders	Myocarditis[d,f]	N/A[g]
	Pericarditis[d,f]	N/A[g]
Gastrointestinal disorders	Diarrhea[d]	248/1826 (13.6%)[b]
	Vomiting[d]	117/1826 (6.4%)[b]
	Nausea	2/1835 (0.1%)[a]
Skin and subcutaneous tissue disorders	Hyperhidrosis[f]	
	Night sweats[f]	
Musculoskeletal and connective tissue disorders	Myalgia (muscle pain)	92/1826 (5.0%)[b]
	Arthralgia (joint pain) (new)	44/1826 (2.4%)[b]
	Pain in extremity (arm)[d]	3/1835 (0.2%)[a]
General disorders and administration site conditions	Injection site pain	858/1826 (47.0%)[c]
	Fatigue	818/1826 (44.8%)[b]
	Injection site redness	346/1833 (18.9%)[c]
	Pyrexia	192/1832 (10.5%)[b]
	Injection site swelling	154/1833 (8.4%)[c]
	Chills	104/1826 (5.7%)[b]
	Asthenia	1/1835 (0.1%)[a]
	Malaise[f]	

a. Source: Number (%) of Participants Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 3, by System Organ Class and Preferred Term – Phase 2/3 – Blinded Placebo-Controlled Follow-Up Period – 2 to <5 Years of Age – Safety Population (Study C4591007, Cutoff date: 29Apr2022)
b. Source = Systemic Events, by Maximum Severity, Within 7 Days After Each Dose –Phase 2/3 – Blinded Placebo Controlled Follow-Up Period – 2 to <5 Years of Age – Safety Population (Study C4591007, Cutoff date: 06Sep2021)
c. Source = Local Reactions, by Maximum Severity, Within 7 Days After Each Dose –Phase 2/3 – Blinded Placebo-Controlled Follow-Up Period – 2 to <5 Years of Age – Safety Population (Study C4591007, Cutoff date: 29Apr2022)
d. These adverse reactions were identified in the post-authorization period.
e. The frequency of rash was calculated as follows: Rash (n=4), Rash erythematous (n=1), Rash maculo-papular (n=1) (4+1+1=6/1835=0.3%).
f. At the time of the data-lock the following reactions were not reported in participants 2 to <5 Years of Age in Study C4591007: pruritus, angioedema, lethargy, myocarditis, pericarditis, hyperhidrosis, night sweats, and malaise.
g. Due to the cross-over design of clinical trials, the actual incidence of myocarditis and pericarditis cannot be reliably estimated however, based on published literature presented in the Clinical Overview, the CIOMS frequency category for myocarditis and pericarditis is "very rare."[89]

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Table A-5. Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency Within Each System Organ Class: Individuals 6 Months to <2 Years of Age (29 April 2022 Data Cut-off Date)[64]

System Organ Class	ADR Term	Frequency n/N (%)
Blood and lymphatic system disorders	Lymphadenopathy	2/1178 (0.2%)[a]
Immune system disorders	Anaphylaxis[d]	Not known
	Hypersensitivity reactions	
	Rash[d,e]	13/1178 (1.1%)[a]
	Urticaria[d]	8/1178 (0.7%)[a]
	Pruritis[d,f]	
	Angioedema[d,f]	
Metabolism and nutrition disorders	Decreased appetite	451/1169 (38.6%)[b]
Psychiatric disorders	Irritability	800/1169 (68.4%)[b]
Nervous system disorders	Headache	2/1178 (0.2%)[a]
	Lethargy	1/1178 (0.1%)[a]
Cardiac disorders	Myocarditis[d,f]	N/A[g]
	Pericarditis[d,f]	N/A[g]
Gastrointestinal disorders	Vomiting[d]	47/1178 (4.0%)[a]
	Diarrhea[d]	39/1178 (3.3%)[a]
	Nausea[f]	
Skin and subcutaneous tissue disorders	Hyperhidrosis[f]	
	Night sweats[f]	
Musculoskeletal and connective tissue disorders	Myalgia (muscle pain)[f]	
	Arthralgia (joint pain) (new)[f]	
	Pain in extremity (arm)[d,f]	
General disorders and administration site conditions	Injection site tenderness	309/1169 (26.4%)[c]
	Injection site redness	210/1177 (17.8%)[c]
	Pyrexia	169/1177 (14.4%)[b]
	Injection site swelling	86/1177 (7.3%)[c]
	Fatigue	8/1178 (0.7%)[a]
	Chills	1/1178 (0.1%)[a]
	Malaise[f]	
	Asthenia[f]	

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Table A-5. Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency Within Each System Organ Class: Individuals 6 Months to <2 Years of Age (29 April 2022 Data Cut-off Date)[64]

a. Source: Number (%) of Participants Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 3, by System Organ Class and Preferred Term – Phase 2/3 – Blinded Placebo-Controlled Follow-Up Period – 6 months to <2 Years of Age – Safety Population (Study C4591007, Cutoff date: 29Apr2022)
b. Source = Systemic Events, by Maximum Severity, Within 7 Days After Each Dose –Phase 2/3 – Blinded Placebo-Controlled Follow-Up Period – 6 months to <2 Years of Age – Safety Population (Study C4591007, Cutoff date: 29Apr2022)
c. Source = Local Reactions, by Maximum Severity, Within 7 Days After Each Dose –Phase 2/3 – Blinded Placebo-Controlled Follow-Up Period – 6 months to <2 Years of Age – Safety Population (Study C4591007, Cutoff date: 29Apr2022)
d. These adverse reactions were identified in the post-authorization period.
e. The frequency of rash was calculated as follows: Rash (n=8), Rash macular (n=1), Rash maculo-papular (n=2); Rash papular (n=1); Rash erythematous (n=1) (8+1+2+1+1=13/1178=1.1%)
f. At the time of the data cut-off date, the following reactions were not reported in participants 6 months to <2 Years of Age in Study C4591007: pruritus, angioedema, myocarditis, pericarditis, nausea, hyperhidrosis, night sweats, myalgia, arthralgia, pain in extremity, malaise, and asthenia.
g. Due to the cross-over design of clinical trials, the actual incidence of myocarditis and pericarditis cannot be reliably estimated however, based on published literature presented in the Clinical Overview, the CIOMS frequency category for myocarditis and pericarditis is "very rare."[89]

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Table A-6. Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency Within Each System Organ Class: BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) – Booster Safety Population (17 June 2021 Data Cut-off Date)[*,64]

System Organ Class	ADR Term	Frequency n/N (%)
Blood and lymphatic system disorders	Lymphadenopathy	16/306 (5.2%)[a,b]
Immune system disorders	Anaphylaxis[e]	Not known
	Hypersensitivity reactions	
	Rash[e]	1/306 (0.3%)[b]
	Pruritus[e,f]	
	Urticaria[e,f]	
	Angioedema[e,f]	
Metabolism and nutrition disorders	Decreased appetite	1/306 (0.3%)[b]
Nervous system disorders	Headache	140/289 (48.4%)[c]
	Lethargy[f]	
Cardiac disorders	Myocarditis[e]	N/A[g]
	Pericarditis[e]	N/A[g]
Gastrointestinal disorders	Diarrhea[e]	25/289 (8.7%)[c]
	Vomiting[e]	5/289 (1.7%)[c]
	Nausea	2/306 (0.7%)[b]
Skin and subcutaneous tissue disorders	Hyperhidrosis[f]	
	Night sweats[f]	
Musculoskeletal and connective tissue disorders	Myalgia (muscle pain)	113/289 (39.1%)[c]
	Arthralgia (joint pain) (new)	73/289 (25.3%)[c]
	Pain in extremity (arm)[e]	1/306 (0.3%)[b]
General disorders and administration site conditions	Injection site pain	240/289 (83.0%)[d]
	Fatigue	184/289 (63.7%)[c]
	Chills	84/289 (29.1%)[c]
	Pyrexia	25/289 (8.7%)[c]
	Injection site swelling	23/289 (8.0%)[d]
	Injection site redness	17/289 (5.9%)[d]
	Malaise[f]	
	Asthenia[f]	

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

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

b. Source: Number (%) of Subjects Reporting at Least 1 Adverse Event From Booster Dose to 1 Month After Booster Dose, by System Organ Class and Preferred Term – Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) – Booster Safety Population (Study C4591001, Cut-off date: 17June2021).

c. Source = Systemic Events, by Maximum Severity, Within 7 Days After Booster Dose Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) – Booster Safety Population (Study C4591001, Cut-off date: 17June2021).

d. Source = Local Reactions, by Maximum Severity, Within 7 Days After Booster Dose – Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) –Booster Safety Population (Study C4591001, Cut-off date: 17June2021).

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

f. The following reactions were not reported in the booster safety population in Study C4591001: angioedema, pruritus, urticaria, malaise, lethargy, asthenia, hyperhidrosis, and night sweats.

g. Due to the cross-over design of clinical trials, the actual incidence of myocarditis and pericarditis cannot be reliably estimated however, based on published literature presented in the Clinical Overview, the CIOMS frequency category for myocarditis and pericarditis is “very rare.”[89]

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Table A-7. Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency Within Each System Organ Class: BNT162b2-Experienced Subjects (≥16 Years of Age) Who Received 1 Booster Dose of BNT162b2 (30 µg) in Study C4591031 – Booster Safety Population (5 October 2021 Data Cut-off Date)[64,80]

System Organ Class	ADR Term	Frequency n/N (%)
Blood and lymphatic system disorders	Lymphadenopathy[a]	141/5055 (2.8%)b
Immune system disorders	Anaphylaxis[c]	Not known
	Hypersensitivity reactions	
	Rash[c]	3/5055 (0.1%)b
	Pruritus[c]	3/5055 (0.1%)[b]
	Urticaria[c]	2/5055 (0.04%)[b]
	Angioedema[c,d]	
Metabolism and nutrition disorders	Decreased appetite	9/5055 (0.2%)[b]
Nervous system disorders	Headache[e]	
	Lethargy	12/5055 (0.2%)[b]
Cardiac disorders	Myocarditis[c]	N/A[f]
	Pericarditis[c]	N/A[f]
Gastrointestinal disorders	Diarrhea[c,e]	
	Vomiting[c,e]	
	Nausea	48/5055 (0.9%)[b]
Skin and subcutaneous tissue disorders	Night sweats	5/5055 (0.1%)[b]
	Hyperhidrosis	4/5055 (0.1%)[b]
Musculoskeletal and connective tissue disorders	Myalgia (muscle pain)[e]	
	Arthralgia (joint pain) (new)[e]	
	Pain in extremity (arm)[c]	54/5055 (1.1%)[b]
General disorders and administration site conditions	Injection site pain[e]	
	Fatigue[e]	
	Chills[e]	
	Pyrexia[e,g]	
	Injection site swelling[e]	
	Injection site redness[e]	
	Malaise	35/5055 (0.7%)[b]
	Asthenia	8/5055 (0.2%)[b]

a. A higher frequency of lymphadenopathy (2.8% vs. 0.4%) was observed in participants receiving a booster dose (in Study C4591031) compared to participants receiving 2 doses. The frequency of lymphadenopathy was calculated as follows: Lymphadenopathy (n=135), Lymph node pain (n=4), Lymphadenitis (n=2) (135+4+2=141/5055=2.8%).
b. Source: Number (%) of Participants Reporting at Least 1 Adverse Event From Booster Vaccination to 1 Month After Booster Vaccination, by System Organ Class and Preferred Term – Blinded Follow-up Period – Safety Population (Study C4591031, Cut-off date: 05October2021).
c. These adverse reactions were identified in the post-authorization period.
d. The following reaction was not reported in the Study C4591031: angioedema.
e. Please see Table A-4 for the frequency of the following reactogenicity adverse reactions that were reported in the booster safety population of Study C4591001: headache, diarrhea, vomiting, myalgia (muscle pain), arthralgia (joint pain) (new), injection site pain, fatigue, chills, pyrexia, injection site swelling, injection site redness.
f. Due to the cross-over design of clinical trials, the actual incidence of myocarditis and pericarditis cannot be reliably estimated however, based on published literature presented in the Clinical Overview, the CIOMS frequency category for myocarditis and pericarditis is "very rare."[89]
g. The preferred term pyrexia is a cluster term also covering 'body temperature increased'.

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Table A-8. Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency Within Each System Organ Class: Individuals 5 Through <12 Years of Age Who Received a Booster Dose (Dose 3) of BNT162b2 (22March2022 Data Cut-off Date)[*,64,84]

System Organ Class	ADR Term	Frequency n/N (%)
Blood and lymphatic system disorders	Lymphadenopathy[a]	10/401 (2.5%)[b]
Immune system disorders	Anaphylaxis[e]	Not known
	Hypersensitivity reactions	
	Rash[e]	1/401 (0.2%)[b]
	Urticaria[e,f]	
	Pruritus[e,f]	
	Angioedema[e,f]	
Metabolism and nutrition disorders	Decreased appetite[f]	
Nervous system disorders	Headache	126/371 (34.0%)[c]
	Lethargy[f]	
Cardiac Disorders	Myocarditis[e,f]	N/A[g]
	Pericarditis[e,f]	N/A[g]
Gastrointestinal disorders	Diarrhea[e]	18/371 (4.9%)[c]
	Vomiting[e]	9/371 (2.4%)[c]
	Nausea[f]	
Skin and subcutaneous tissue disorders	Hyperhidrosis[f]	
	Night sweats[f]	
Musculoskeletal and connective tissue disorders	Myalgia (muscle pain)	68/371 (18.3%)[c]
	Arthralgia (joint pain) (new)	25/371 (6.7%)[c]
	Pain in extremity (arm)[e,f]	
General disorders and administration site conditions	Injection site pain	274/371 (73.9%)[d]
	Fatigue	169/371 (45.6%)[c]
	Injection site swelling	61/371 (16.4%)[d]
	Injection site redness	58/371 (15.6%)[d]
	Chills	39/371 (10.5%)[c]
	Pyrexia	25/371 (6.7%)[c]
	Malaise[f]	
	Asthenia[f]	

* Booster dose (Dose 3) of BNT162b2 10 µg was administered to participants 5 through <12 years of age in Study C4591007.

a. A higher frequency of lymphadenopathy was observed in participants 5 through <12 years of age in Study C4591007 (2.5% vs. 0.9%) receiving a booster dose compared to participants receiving 2 doses. The frequency of lymphadenopathy was calculated as follows: lymphadenopathy (n = 8), lymph node palpable (n = 1), axillary mass (n = 1) (8+1+1 = 10/401 = 2.5%).

b. Source: Number (%) of Participants Reporting at Least 1 Adverse Event From Dose 3 to 1 Month After Dose 3, by System Organ Class and Preferred Term – Phase 2/3 – Participants Who Received Dose 3 of BNT162b2 – 5 to <12 Years of Age – Safety Population (Study C4591007, Cut-off date: 22March2022).

c. Source = Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Phase 2/3 – Participants Who Received Dose 3 of BNT162b2 – 5 to <12 Years of Age – Safety Population (Study C4591007, Cut-off date: 22March2022).

d. Source = Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Phase 2/3 – Participants Who Received Dose 3 of BNT162b2 – 5 to <12 Years of Age – Safety Population (Study C4591007, Cut-off date: 22March2022).

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

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f. At the time of the data cut-off date, the following reactions were not reported in participants 5 through <12 Years of Age in Study C4591007 after Dose 3: urticaria, pruritus, angioedema, decreased appetite, lethargy, myocarditis, pericarditis, nausea, night sweats, hyperhidrosis, pain in extremity (arm), malaise, asthenia.

g. Due to the cross-over design of clinical trials, the actual incidence of myocarditis and pericarditis cannot be reliably estimated however, based on published literature presented in the Clinical Overview, the CIOMS frequency category for myocarditis and pericarditis is "very rare."[89]

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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

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)[64]

System Organ Class	Very Common ≥1/10 (≥10%)	Common ≥1/100 to <1/10 (≥1% to <10%)	Uncommon ≥1/1,000 to <1/100 (≥0.1% to <1%)	Rare ≥1/10,000 to <1/1,000 (≥0.01% to <0.1%)	Very Rare <1/10,000 (<0.01%)	Frequency not known (cannot be estimated from the available data)
Blood and lymphatic system disorders			Lymphadenopathy			
Immune system disorders			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			
Cardiac disorders					Myocarditis[a]; Pericarditis[a]	
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			

* CIOMS frequency categories are based on clinical trial C4591001 crude incidence and was reported to only one significant figure.

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.

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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)[64]

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

* CIOMS frequency categories are based on clinical trial C4591001 crude incidence and was reported to only one significant figure.

a. These adverse reactions were identified in the post-authorization period. The following events were not reported in the 12 through 15 years of age group in Study C4591001: angioedema, pruritus, malaise, lethargy, asthenia, decreased appetite, hyperhidrosis, and night sweats.

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

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Table B-3. ADRs by System Organ Class and CIOMS Frequency Category* Listed in Order of Decreasing Medical Seriousness Within Each Frequency Category and System Organ Class: Individuals 5 Through <12 Years of Age (06 September 2021 Data Cut-off Date)[64]

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

* CIOMS frequency categories are based on clinical trial C4591007 crude incidence and was reported to only one significant figure.

a. These adverse reactions were identified in the post-authorization period. At the time of the data cut-off date, the following reactions were not reported in participants 5 through <12 years of age in Study C4591007: angioedema, lethargy, myocarditis, pericarditis, asthenia, hyperhidrosis, and night sweats.

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

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Table B-4. ADRs by System Organ Class and CIOMS Frequency Category* Listed in order of Decreasing Medical Seriousness Within Each Frequency Category and System Organ Class: Individuals 2 to <5 Years of Age (29 April 2022 Data Cut-off Date)[64]

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

* CIOMS frequency categories are based on clinical trial C4591007 crude incidence and was reported to only one significant figure.

a. These adverse reactions were identified in the post-authorization period. At the time of the data cut-off date, the following reactions were not reported in participants 2 to <5 Years of Age in Study C4591007: pruritus, angioedema, lethargy, myocarditis, pericarditis, hyperhidrosis, night sweats, and malaise.

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

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Table B-5. ADRs by System Organ Class and CIOMS Frequency Category* Listed in Order of Decreasing Medical Seriousness Within Each Frequency Category and System Organ Class: Individuals 6 Months to <2 Years of Age (29 April 2022 Data Cut-off Date)[64]

System Organ Class	Very Common ≥1/10 (≥10%)	Common ≥1/100 to <1/10 (≥1% to <10%)	Uncommon ≥1/1,000 to <1/100 (≥0.1% to <1%)	Rare ≥1/10,000 to <1/1,000 (≥0.01% to <0.1%)	Very Rare <1/10,000 (<0.01%)	Frequency not known (cannot be estimated from the available data)
Blood and lymphatic system disorders			Lymphadenopathy			
Immune system disorders		Rash[a,b]	Urticaria[a,b]			Anaphylaxis[a]
Metabolism and nutrition disorders	Decreased appetite					
Psychiatric disorders	Irritability					
Nervous system disorders			Headache Lethargy			
Gastrointestinal disorders		Vomiting[a,] Diarrhea[a]				
General disorders and administration site conditions	Injection site tenderness; Injection site redness; Pyrexia	Injection site swelling	Fatigue; Chills			

* CIOMS frequency categories are based on clinical trial C4591007 crude incidence and was reported to only one significant figure.

a. These adverse reactions were identified in the post-authorization period. At the time of the data-lock, the following reactions were not reported in participants 6 months to <2 Years of Age in Study C4591007: pruritus, angioedema, nausea, hyperhidrosis, night sweats, myalgia, arthralgia, pain in extremity, malaise, and asthenia.

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

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Table B-6. ADRs by SOC and CIOMS Frequency Category* Listed in Order of Decreasing Medical Seriousness Within Each Frequency Category and SOC: BNT162b2-Experienced Individuals Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) – Booster Safety Population (17 June 2021 Data Cut-off Date)†,[64]

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

* CIOMS frequency categories are based on clinical trial C4591001 crude incidence and was reported to only one significant figure.

† The booster dose of BNT162b2 30 µg was administered to participants 18 to 55 years of age.

a. These adverse reactions were identified in the post-authorization period. The following events were not reported in the booster safety population in Study C4591001: angioedema, pruritus, urticaria, malaise, lethargy, asthenia, hyperhidrosis, and night sweats.

b. The following event is categorized as a hypersensitivity reaction: rash.

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Table B-7. ADRs by System Organ Class and CIOMS Frequency Category* Listed in Order of Decreasing Medical Seriousness Within Each Frequency Category and System Organ Class: Study C4591031† (5 October 2021 Data Cut-off Date)[64]

System Organ Class	Very Common ≥1/10 (≥10%)	Common ≥1/100 to <1/10 (≥1% to <10%)	Uncommon ≥1/1,000 to <1/100 (≥0.1% to <1%)	Rare ≥1/10,000 to <1/1,000 (≥0.01% to <0.1%)	Very Rare <1/10,000 (<0.01%)	Frequency not known (cannot be estimated from the available data)
Blood and lymphatic system disorders		Lymphadenopathy				
Immune system disorders			Pruritus[a,b]; Rash[a,b]	Urticaria[a,b]		Anaphylaxis[a]
Metabolism and nutrition disorders			Decreased appetite			
Nervous system disorders			Lethargy			
Cardiac disorders					Myocarditis[a]; Pericarditis[a]	
Gastrointestinal disorders			Nausea			
Skin and subcutaneous tissue disorders			Hyperhidrosis; Night sweats			
Musculoskeletal and connective tissue disorders		Pain in extremity (arm)[a]				
General disorders and administration site conditions			Asthenia; Malaise			

* CIOMS frequency categories are based on clinical trial C4591031 crude incidence and was reported to only one significant figure.

† Study C4591031 included individuals 16 years of age and older.

Please see Table B-4 for the CIOMS Frequency Categories for the following reactogenicity adverse reactions that were reported in the booster safety population of Study C4591001: headache, diarrhea, vomiting, myalgia (muscle pain), arthralgia (joint pain) (new), injection site pain, fatigue, chills, pyrexia, injection site swelling, injection site redness.

The preferred term pyrexia is a cluster term also covering 'body temperature increased'.

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

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

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Table B-8. ADRs by System Organ Class and CIOMS Frequency Category* Listed in Order of Decreasing Medical Seriousness Within Each Frequency Category and System Organ Class: Individuals 5 Through <12 Years of Age Who Received Dose 3 (22March2022 Data Cut-off Date)†,64,84

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

* CIOMS frequency categories are based on clinical trial C4591007 crude incidence and was reported to only one significant figure.

† Dose 3 (a booster dose) of BNT162b2 10 µg was administered to participants 5 through <12 years of age in Study C4591007.

a. These adverse reactions were identified in the post-authorization period. At the time of the data cut-off date, the following reactions were not reported in participants 5 through <12 years of age in Study C4591007 after Dose 3: urticaria, pruritus, angioedema, decreased appetite, lethargy, myocarditis, pericarditis, nausea, night sweats, hyperhidrosis, pain in extremity (arm), malaise, and asthenia.

b. The following event is categorized as a hypersensitivity reaction: rash.

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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.

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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

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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 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.

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PREPARED BY PFIZER INC

CDS EFFECTIVE DATE: 31-AUG-2022

Date of Superseded CDS: 26-July-2022

COVID-19 mRNA Vaccine

CORE DATA SHEET

VERSION 15

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1. NAME OF THE MEDICINAL PRODUCT

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

{{COMIRNATY Bivalent Original and Omicron BA.1 15/15 micrograms per dose is called TRADENAME (Bivalent)}}.

{{COMIRNATY Bivalent Original and Omicron BA.4/BA.5 15/15 micrograms per dose is called TRADENAME (Bivalent)}}.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION[1,2,72,85,120]

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

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

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

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

For the full list of excipients, see Section 6.1.

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

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

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

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

For the full list of excipients, see Section 6.1.

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

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

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

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

For the full list of excipients, see Section 6.1.

*[Editorial guidance for countries: Select this text for the **Tris/Sucrose presentation, 3 micrograms/dose**.]*

TRADENAME (for age 6 months to <5 years): This is a multidose vial and must be diluted before use. One vial (0.4 mL) contains 10 doses of 0.2 mL after dilution (see Sections 4.2 and 6.6).

One dose (0.2 mL) contains 3 micrograms of COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

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

For the full list of excipients, see Section 6.1.

*[Editorial guidance for countries: Select this text for the **Bivalent (Original/Omicron) presentation, 15/15 micrograms/dose**.]*

TRADENAME (Bivalent): This is a multidose vial and must be diluted before use. One vial (2.25 mL) contains 6 doses of 0.3 mL (see Sections 4.2 and 6.6).

One dose (0.3 mL) contains 15/15 micrograms of COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

TRADENAME (Bivalent) 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) (Original and {{Omicron BA.1}} {{Omicron BA.4/BA.5}}).

For the full list of excipients, see Section 6.1.

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3. PHARMACEUTICAL FORM[2,3,72,85]

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

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

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

TRADENAME (Do Not Dilute): Dispersion for injection.

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

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

*[Editorial guidance for countries: Select this text for the **Tris/Sucrose presentation, 3 micrograms/dose**.]*

TRADENAME (for age 6 months to <5 years): Concentrate for dispersion for injection.

*[Editorial guidance for countries: Select this text for the **Bivalent (Original/Omicron) presentation, 15/15 micrograms/dose**.]*

TRADENAME (Bivalent): Dispersion for injection.

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

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

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

Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 virus, in individuals 6 months of age and older.[4,49,73,86]

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4.2. Posology and method of administration

Posology

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

Individuals 12 years of age and older

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

Booster dose in individuals 12 years of age and older

A booster dose of TRADENAME (Dilute Before Use) or TRADENAME (Do Not Dilute) may be administered intramuscularly at least 5 months after the second dose in individuals 12 years of age and older.[71,87]

Subsequent doses of TRADENAME (Dilute Before Use) or TRADENAME (Do Not Dilute) may be administered to individuals 12 years of age and older at least 4 months after a previous booster dose of TRADENAME.[121]

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

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

Interchangeability

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

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

For further information on efficacy, see Section 5.1.

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

Individuals 5 through <12 years of age

TRADENAME (for age 5 years to <12 years) is administered intramuscularly after dilution as a primary series of 2 doses (0.2 mL) at greater than or equal to 21 days (preferably 3 weeks) apart.[73]

Booster dose in individuals 5 through <12 years of age

A booster dose of TRADENAME (for age 5 years to <12 years of age) may be administered intramuscularly at least 6 months after the second dose in individuals 5 years through <12 years of age.[84]

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

Interchangeability

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

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

For further information on efficacy, see Section 5.1.

*[Editorial guidance for countries: Select this text for the **Tris/Sucrose presentation, 3 micrograms/dose**.]*

Individuals 6 months through <5 years of age

TRADENAME (for age 6 months to <5 years) is administered intramuscularly after dilution as a primary series of 3 doses (0.2 mL). The initial 2 doses are administered 3 weeks apart followed by a third dose administered at least 8 weeks after the second dose.[86]

Individuals who will turn from 4 years to 5 years of age between their doses in the vaccination series should receive their age-appropriate dose at the time of the vaccination and the interval between doses is determined by the individual's age at the start of the vaccination series.[88]

TRADENAME (for age 6 months to <5 years) cannot be used in individuals 5 years of age and older.

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Interchangeability

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

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

For further information on efficacy, see Section 5.1.

*[Editorial guidance for countries: Select this text for the **Bivalent (Original/Omicron) presentation, 15/15 micrograms/dose**.]*

Booster dose in individuals 12 years of age and older

A booster dose of TRADENAME (Bivalent) may be administered intramuscularly at least 5 months after completing the primary series of TRADENAME. Subsequent doses of TRADENAME (Bivalent) may be administered to individuals 12 years of age and older at least 4 months after a previous booster dose of TRADENAME or TRADENAME (Bivalent).

For further information on efficacy, see Section 5.1.

Pediatric population

The safety and efficacy of TRADENAME in individuals under 6 months of age have not yet been established. The safety and effectiveness of a booster dose of TRADENAME in individuals 16 through 17 years of age is based on safety and effectiveness data in adults at least 18 through 55 years of age.[71,86]

{{The safety and efficacy of TRADENAME (Bivalent) in children less than 12 years of age has 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]

The safety of a booster dose of TRADENAME in individuals 65 years of age and older is based on safety data in 12 booster dose recipients 65 through 85 years of age in Study 2, 306 booster dose recipients 18 through 55 years of age in Study 2, and 1,175 booster dose recipients 65 years of age and older in Study 4. The effectiveness of a booster dose of TRADENAME in individuals 65 years of age and older is based on effectiveness data in 306 booster dose recipients 18 through

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55 years of age in Study 2, and an efficacy analysis from participants 16 years of age and older in 9,945 participants in Study 4.[71, 80]

Method of administration

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

Administer TRADENAME intramuscularly in the deltoid muscle.

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

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

Individuals 12 years of age and older

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

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

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

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

Administer TRADENAME intramuscularly in the deltoid muscle.

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

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

Individuals 12 years of age and older

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

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

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

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

Administer TRADENAME intramuscularly in the deltoid muscle.

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

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

Individuals 5 through <12 years of age

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

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

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

*[Editorial guidance for countries: Select this text for the **Tris/Sucrose presentation, 3 micrograms/dose**.]*

In individuals 6 to less than 12 months of age, administer TRADENAME intramuscularly in the anterolateral aspect of the thigh. In individuals 1 years of age and older, administer TRADENAME intramuscularly in the anterolateral aspect of the thigh or the deltoid muscle.

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

After dilution, vials of TRADENAME (for age 6 months to <5 years) contains 10 doses of 0.2 mL of vaccine.

Individuals 6 months through <5 years of age

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

- Each dose must contain 0.2 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.2 mL, discard the vial and content.

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- Do not pool excess vaccine from multiple vials.

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

*[Editorial guidance for countries: Select this text for the **Bivalent (Original/Omicron) presentation, 15/15 micrograms/dose**.]*

Administer TRADENAME (Bivalent) intramuscularly in the deltoid muscle.

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

Vials of TRADENAME (Bivalent) contain 6 doses of 0.3 mL of vaccine.

Individuals 12 years of age and older

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

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

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

4.3. Contraindications

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

4.4. Special warnings and precautions for use

Traceability

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

General recommendations

As with all injectable vaccines, appropriate medical treatment and supervision must always be readily available in case of a rare anaphylactic event following the administration of the vaccine.[9]

Very rare cases of myocarditis and pericarditis have been reported following vaccination with TRADENAME. Typically, the cases have occurred more often in younger men and after the second dose of the vaccine and within 14 days after vaccination. Based on accumulating data, the

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reporting rates of myocarditis and pericarditis after primary series in children ages 5 through <12 years are lower than in ages 12 through 17 years. Rates of myocarditis and pericarditis in booster doses do not appear to be higher than after the second dose in the primary series. The cases are generally mild and individuals tend to recover within a short time following standard treatment and rest. Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis in vaccine recipients.[69,89]

The administration of TRADENAME {{or TRADENAME (Bivalent)}} 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 {{or TRADENAME (Bivalent)}} 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 {{or TRADENAME (Bivalent)}} 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.

{{No data are available yet regarding the use of TRADENAME (Bivalent) during pregnancy.}}

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Lactation

It is unknown whether TRADENAME is excreted in human milk.

{{No data are available yet regarding the use of TRADENAME (Bivalent) during breast-feeding.}}

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]

{{It is unknown whether TRADENAME (Bivalent) has an impact on fertility.}}

4.7. Effects on ability to drive and use machines

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

4.8. Undesirable effects

Summary of safety profile

The safety of TRADENAME was evaluated in participants 5 years of age and older in 3 clinical studies conducted in the United States, Europe, Turkey, South Africa, and South America.[12,49] Study BNT162-01 (Study 1) enrolled 60 participants, 18 through 55 years of age and 36 participants, 56 through 85 years of age.[68] Study C4591001 (Study 2) enrolled approximately 46,000 participants,[41] 12 years of age or older.[12] Study C4591007 (Study 3) enrolled approximately 2,300 participants 5 through <12 years of age.[73] Study 3 also enrolled approximately 1,800 participants 2 through 4 years of age and 1,200 participants 6 months through 23 months of age.[86]

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

In Study C4591031 (Study 4), a placebo-controlled booster study, 5,081 participants 16 years of age and older were recruited from Study 2 to receive a booster dose of TRADENAME at least 6 months after the second dose. The overall safety profile for the booster dose was similar to that seen after 2 doses.[80]

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In a subset of Study 3 (Phase 2/3) participants, 401 participants 5 through <12 years of age received a booster dose of TRADENAME at least 5 months after completing the primary series. The overall safety profile for the booster dose was similar to that seen after the primary series.[84]

Participants 16 years of age and older – after 2 doses

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

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

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

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

Adolescents 12 through 15 years of age – after 2 doses[81]

In an analysis of long-term safety follow-up in Study 2, 2,260 adolescents (1,131 TRADENAME; 1,129 placebo) were 12 through 15 years of age. Of these, 1,559 adolescents (786 TRADENAME and 773 placebo) have been followed for ≥4 months after the second dose.[41,42] The safety evaluation in Study 2 is ongoing.

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

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

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

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

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Children 2 through 4 years of age – after 3 doses[90,91,92]

In an analysis of Study 3 (Phase 2/3), 2,750 individuals (1,835 TRADENAME 3 mcg and 915 placebo) were 2 through 4 years age. Based on data in the blinded placebo-controlled follow-up period up to the cutoff date of April 29, 2022, 886 individuals 2 through 4 years of age who received a 3-dose primary course (606 TRADENAME 3 mcg and 280 placebo) have been followed a median of 1.4 months after the third dose.

The most frequent adverse reactions in children 2 through 4 years of age that received any primary series dose included pain at injection site and fatigue (>40%), injection site redness and fever (>10%).

Children 6 through 23 months of age – after 3 doses[93,94,95]

In an analysis of Study 3 (Phase 2/3), 1,776 individuals (1,178 TRADENAME 3 mcg and 598 placebo) were 6 through 23 months of age. Based on data in the blinded placebo-controlled follow-up period up to the cutoff date of April 29, 2022, 570 individuals 6 through 23 months of age who received a 3-dose primary course (386 TRADENAME 3 mcg and 184 placebo) have been followed for a median of 1.3 months after the third dose.

The most frequent adverse reactions in children 6 through 23 months of age that received any primary series dose included irritability (>60%), decrease appetite (>30%), tenderness at the injection site (>20%), injection site redness and fever (>10%).

Participants 12 years of age and older – after booster dose[71]

The safety of a booster dose of TRADENAME in participants 12 years of age and older is inferred from safety data from studies of a booster dose of TRADENAME in participants 16 years of age and older.

A subset from Study 2 (Phase 2/3) participants of 306 adults at least 18 through 55 years of age who completed the primary TRADENAME 2-dose course, received a booster dose of TRADENAME approximately 6 months (range of 4.8 to 8.0 months) after receiving Dose 2. Of these, 301 participants have been followed for ≥4 months after the booster dose of TRADENAME.[96]

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

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In Study 4, a placebo-controlled booster study, participants 16 years of age and older recruited from Study 2 received a booster dose of TRADENAME (5,081 participants), or placebo (5,044 participants) at least 6 months after the second dose of TRADENAME. Overall, participants who received a booster dose, had a median follow-up time of 2.8 months (range 0.3 to 7.5 months) after the booster dose in the blinded placebo-controlled follow-up period to the cut-off date (8 February 2022).[80,97] Of these, 1281 participants (895 TRADENAME and 386 placebo) have been followed for ≥4 months after the booster dose of TRADENAME.[98]

Participants 12 years of age and older – after subsequent booster doses

The safety of a booster dose of TRADENAME in participants 12 years of age and older is inferred from safety data from studies of a booster dose of TRADENAME in participants 18 years of age and older.

A subset of 325 adults 18 to ≤55 years of age who had completed 3 doses of TRADENAME, received a booster (fourth dose) of TRADENAME (30 mcg) 90 to 180 days after receiving Dose 3.[122,123] Participants who received a booster (fourth dose) of TRADENAME (30 mcg) had a median follow-up time of 1.4 months.[124] The most frequent adverse reactions in these participants were injection site pain (>70%), fatigue (>60%), headache (>40%), myalgia and chills (>20%) and arthralgia (>10%).[125,126]

In a subset from Study 4 (Phase 3), 305 adults greater than 55 years of age who had completed 3 doses of TRADENAME, received a booster (fourth dose) of TRADENAME (30 mcg) 5.3 to 13.1 months after receiving Dose 3.[127,128] Participants who received a booster (fourth dose) of TRADENAME (30 mcg) had a median follow-up time of at least 1.7 months up to a data cutoff date of 16 May 2022.[129] The most frequent adverse reactions in participants greater than 55 years of age were injection site pain (>60%), fatigue (>40%), headache (>20%), myalgia and chills (>10%).[130,131,132]

Omicron-adapted TRADENAME – after a booster dose of TRADENAME (Bivalent, Original/Omicron BA.1) or monovalent Omicron BA.1 (fourth dose)

The safety of a booster dose of TRADENAME (Bivalent) in participants 12 years of age and older is inferred from safety data from studies of a booster dose of TRADENAME (Bivalent Original/Omicron BA.1) in individuals greater than 55 years of age and also safety data from studies of a booster dose of monovalent Omicron BA.1 in individuals 18 to ≤55 years of age.

Participants greater than 55 years of age – after a booster dose of TRADENAME (Bivalent, Original/Omicron BA.1)

In a subset from Study 4 (Phase 3), 305 adults greater than 55 years of age who had completed 3 doses of TRADENAME, received a booster (fourth dose) of TRADENAME (Bivalent, Original/Omicron BA.1) 15/15 mcg 4.7 to 11.5 months after receiving Dose 3.[133,134,135] Participants who received a booster (fourth dose) of TRADENAME (Bivalent, Original/Omicron BA.1) had a median follow-up time of at least 1.7 months up to a data cutoff date of 16 May 2022.[136,137]

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The overall safety profile for the TRADENAME (Bivalent, Original/Omicron BA.1) booster (fourth dose) was similar to that seen after the TRADENAME booster (third dose). The most frequent adverse reactions in participants greater than 55 years of age were injection site pain (>50%), fatigue (>40%), headache (>30%), myalgia (>20%), chills and arthralgia (>10%). No new adverse reactions were identified for TRADENAME (Bivalent, Original/Omicron BA.1).[138,139]

Participants 18 to ≤55 years of age – after a booster dose of monovalent Omicron BA.1

A subset of 315 adults 18 to ≤55 years of age who had completed 3 doses of TRADENAME, received a booster (fourth dose) of Omicron BA.1 30 mcg (monovalent) 90 to 180 days after receiving Dose 3.[122,123] Participants who received a booster (fourth dose) of monovalent Omicron BA.1 had a median follow-up time of 1.4 months.[124] The most frequent adverse reactions in these participants were injection site pain (>70%), fatigue (>60%), headache (>40%), myalgia (>30%), chills (>30%) and arthralgia (>20%).[125,126]

Children 5 through <12 years of age – after booster dose[84]

In a subset from Study 3, a total of 401 children 5 through <12 years of age received a booster dose of TRADENAME 10 mcg at least 5 months (range of 5 to 9 months) after completing the primary series. The analysis of the Study 3 (Phase 2/3) subset is based on data up to the cut-off date of March 22, 2022 (median follow-up time of 1.3 months).

The most frequent adverse reactions in participants 5 through <12 years of age were injection site pain (>70%), fatigue (>40%), headache (>30%), myalgia, chills, injection site redness, and swelling (>10%).

The adverse reactions in the tables below apply to TRADENAME and TRADENAME (Bivalent) and all age groups unless specified otherwise.

Table 1. Adverse Drug Reactions (Clinical Trials)[13,14,16,64,80,86]

System Organ Class	Adverse Drug Reactions
Blood and lymphatic system disorders	Lymphadenopathy[a]
Metabolism and nutrition disorders	Decreased appetite
Psychiatric disorders	Irritability[c]
Nervous system disorders	Headache Lethargy
Gastrointestinal disorders	Nausea
Skin and subcutaneous tissue disorders	Hyperhidrosis Night sweats
Musculoskeletal and connective tissue disorders	Arthralgia Myalgia

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System Organ Class	Adverse Drug Reactions
General disorders and administration site conditions	Pyrexia[b] Chills Asthenia Malaise Fatigue Injection site pain Injection site tenderness[c] Injection site swelling Injection site redness

a. A higher frequency of lymphadenopathy was observed in participants 5 through <12 years of age in Study 3 (2.5% vs. 0.9%) and in participants 16 years of age and older in Study 4 (2.8% vs. 0.4%) receiving a booster dose compared to participants receiving 2 doses.[71,84]
b. A higher frequency of pyrexia was observed after the second dose compared to the first dose. The preferred term pyrexia is a cluster term covering also body temperature increased.
c. Irritability and injection site tenderness pertain to participants 6 through 23 months of age.[86]

Table 2. Adverse Drug Reactions (Post-authorization Experience)[38,64,80,89]

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

a. A higher frequency of pain in extremity (1.1% vs. 0.8%) was observed in participants receiving a booster dose in Study 4 compared to participants receiving 2 doses.

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.

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

Efficacy

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

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

In the Phase 2/3 portion of Study 2, based on data accrued through 14 November 2020, approximately 44,000 participants 12 years of age and older were randomized equally and received 2 doses of TRADENAME 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 TRADENAME 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.

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

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

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

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At the time of the primary efficacy analysis, participants had been followed for symptomatic COVID-19 for at least 2214 person-years for the TRADENAME 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]

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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.

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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.

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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.

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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)

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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 1,000 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.

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

Subgroup	TRADENAME N[a]=22,166 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=22,320 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]
Sex			
Male	44 3.376 (11,103)	411 3.181 (10,920)	89.9 (86.2, 92.8)
Female	37 3.133 (10,539)	462 3.093 (10,769)	92.1 (88.9, 94.5)
Ethnicity			
Hispanic or Latino	32 1.862 (5408)	245 1.794 (5391)	87.4 (81.8, 91.6)
Not Hispanic or Latino	48 4.615 (16,128)	628 4.445 (16,186)	92.6 (90.1, 94.6)
Race			
Black or African American	4 0.611 (1958)	49 0.601 (1985)	92.0 (78.1, 97.9)
White	69 5.379 (17,801)	768 5.191 (17,880)	91.3 (88.9, 93.3)
All others[f]	8 0.519 (1883)	56 0.481 (1824)	86.8 (72.1, 94.5)
Country			
Argentina	16 1.033 (2655)	110 1.017 (2670)	85.7 (75.7, 92.1)
Brazil	14 0.441 (1419)	82 0.408 (1401)	84.2 (71.9, 91.7)
Germany	0 0.047 (237)	1 0.048 (243)	100.0 (-3868.6, 100.0)
South Africa	0 0.099 (358)	10 0.096 (358)	100.0 (56.6, 100.0)
Turkey	0 0.029 (238)	6 0.026 (232)	100.0 (22.2, 100.0)
United States	51 4.861 (16,735)	664 4.678 (16,785)	92.6 (90.2, 94.6)

Notes: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting). Included confirmed cases in participants 12 through 15 years of age: 0 in the TRADENAME group; 18 in the placebo group.

* Participants who had no evidence of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

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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 Na=18,198 Cases n1b Surveillance Timec (n2d)	Placebo Na=18,325 Cases n1b Surveillance Timec (n2d)	Vaccine Efficacy % (95% CIe)
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)

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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 obese			
16 to 64 and not obese	4 1.107 (8811)	83 1.101 (8825)	95.2 (87.3, 98.7)
16 to 64 and obese	3 0.598 (4734)	60 0.609 (4789)	94.9 (84.4, 99.0)
≥65 and not obese	1 0.343 (2582)	12 0.338 (2567)	91.8 (44.5, 99.8)
≥65 and obese	0 0.165 (1265)	7 0.173 (1313)	100.0 (27.1, 100.0)

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

* Subjects who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

a. N = number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
f. At risk is defined as having at least 1 of the Charlson Comorbidity Index (CMI) category or obesity (BMI ≥30 kg/m^2).
g. Obese is defined as BMI ≥30 kg/m^2.

The updated subgroup analyses of vaccine efficacy by risk status in participants followed up to 6 months after Dose 2 (with a cut-off date of 13 March 2021) are presented in Table 10 and Table 11.

Table 10. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – Participants Without Evidence of Infection* Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period[55]

Subgroup	TRADENAME N[a]=20,998 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=21,096 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]
First COVID-19 occurrence from 7 days after Dose 2[f]	77 6.247 (20,712)	850 6.003 (20,713)	91.3 (89.0, 93.2)

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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]
At risk[g]			
Yes	35 2.797 (9167)	401 2.681 (9136)	91.6 (88.2, 94.3)
No	42 3.450 (11,545)	449 3.322 (11,577)	91.0 (87.6, 93.6)
Age group (years) and risk status			
16 through 64 and not at risk	41 2.776 (8887)	385 2.661 (8886)	89.8 (85.9, 92.8)
16 through 64 and at risk	29 2.083 (6632)	325 1.993 (6629)	91.5 (87.5, 94.4)
65 and older and not at risk	1 0.553 (1870)	53 0.546 (1922)	98.1 (89.2, 100.0)
65 and older and at risk	6 0.680 (2322)	71 0.656 (2304)	91.8 (81.4, 97.1)
Obese[h]			
Yes	27 2.103 (6796)	314 2.050 (6875)	91.6 (87.6, 94.6)
No	50 4.143 (13,911)	536 3.952 (13,833)	91.1 (88.1, 93.5)
Age group (years) and obesity status			
16 through 64 and not obese	46 3.178 (10,212)	444 3.028 (10,166)	90.1 (86.6, 92.9)
16 through 64 and obese	24 1.680 (5303)	266 1.624 (5344)	91.3 (86.7, 94.5)
65 and older and not obese	4 0.829 (2821)	79 0.793 (2800)	95.2 (87.1, 98.7)
65 and older and obese	3 0.404 (1370)	45 0.410 (1426)	93.2 (78.9, 98.7)

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Subgroup	TRADENAME N[a]=20,998 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=21,096 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]

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

* Participants who had no evidence of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

a. N = Number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Two-sided confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.
f. Included confirmed cases in participants 12 through 15 years of age: 0 in the TRADENAME group; 16 in the placebo group.
g. At risk is defined as having at least 1 of the Charlson Comorbidity Index (CMI) category or obesity (BMI ≥30 kg/m^2 or BMI ≥95th percentile [12 through 15 Years of age]).
h. Obese is defined as BMI ≥30 kg/m^2. For 12 through 15 years age group, obesity is defined as a BMI at or above the 95th percentile. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.

Table 11. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – Participants With or Without* Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period[56]

Subgroup	TRADENAME N[a]=22,166 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=22,320 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]
First COVID-19 occurrence from 7 days after Dose 2[f]	81 6.509 (21,642)	873 6.274 (21,689)	91.1 (88.8, 93.0)

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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]
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)

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.

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Subgroup	TRADENAME N[a]=22,166 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=22,320 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]

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

Efficacy against severe COVID-19 - after 2 doses

Secondary efficacy analyses suggested benefit of TRADENAME 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 TRADENAME group and 9 cases in placebo group), with an estimated vaccine efficacy of 75.0% (95% CI: -152.6, 99.5) (1 case in TRADENAME 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 TRADENAME 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)

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

Efficacy and immunogenicity in adolescents 12 to 15 years of age – after 2 doses

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

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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 through 25 years of age who had no serological or virological evidence of past SARS-CoV-2 infection. The immune response to TRADENAME in adolescents 12 to 15 years of age (n=190) was non-inferior to the immune

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response in participants 16 through 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 through 25 years of age group was 1.76, with a 2-sided 95% CI of 1.47 to 2.10, meeting the 1.5-fold non-inferiority criterion (the lower bound of the 2-sided 95% CI for the 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 through 25 years of age.[48]

An updated efficacy analysis of Study 2 has been performed in approximately 2,260 adolescents 12 through 15 years of age evaluating confirmed COVID-19 cases accrued up to a data cut-off date of September 2, 2021, representing up to 6 months of follow-up after Dose 2 for participants in the efficacy population.[81]

The updated vaccine efficacy information in adolescents 12 through 15 years of age is presented in Table 14.

Table 14. 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 Through 15 Years of Age Evaluable Efficacy (7 Days) Population[81]

First COVID-19 occurrence from 7 days after Dose 2 in adolescents 12 through 15 years of age without evidence of prior SARS-CoV-2 infection*			
	TRADENAME N[a]=1057 Cases n1[b] Surveillance Time[c] (n2[d])	**Placebo N[a]=1030 Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI[e])**
Adolescents 12 through 15 years of age	0 0.343 (1043)	28 0.322 (1019)	100.0 (86.8, 100.0)
First COVID-19 occurrence from 7 days after Dose 2 in adolescents 12 through 15 years of age with or without evidence of prior SARS-CoV-2 infection			
	TRADENAME N[a]=1119 Cases n1[b] Surveillance Time[c] (n2[d])	**Placebo N[a]=1109 Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI[e])**
Adolescents 12 through 15 years of age	0 0.362 (1098)	30 0.345 (1088)	100.0 (87.5, 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).

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* 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.

Efficacy in children 5 through <12 years of age – after 2 doses

A descriptive efficacy analysis of Study 3 has been performed in 1,968 children 5 through <12 years of age without evidence of infection prior to 7 days after Dose 2. This analysis evaluated confirmed symptomatic COVID-19 cases accrued up to a data cut-off date of October 8, 2021.[82]

Table 15 presents the specific demographic characteristics in participants who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose.

Table 15. Demographics Characteristics – Participants Without Evidence of Infection Prior to 7 Days After Dose 2 – Phase 2/3 – 5 Through <12 Years of Age – Evaluable Efficacy Population[82]

	TRADENAME 10 mcg/dose (N[a]=1305) n[b] (%)	**Placebo (N[a]=663) n[b] (%)**
Sex		
Male	679 (52.0)	343 (51.7)
Female	626 (48.0)	320 (48.3)
Age at Vaccination		
Mean (SD)	8.2 (1.93)	8.1 (1.98)
Median	8.0	8.0
Min, max	(5, 11)	(5, 11)
Race		
White	1018 (78.0)	514 (77.5)
Black or African American	76 (5.8)	48 (7.2)
American Indian or Alaska Native	<1.0%	<1.0%
Asian	86 (6.6)	46 (6.9)
Native Hawaiian or other Pacific Islander	<1.0%	<1.0%
Other[c]	110 (8.4)	52 (7.8)

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	TRADENAME 10 mcg/dose (N[a]=1305) n[b] (%)	Placebo (N[a]=663) n[b] (%)
Ethnicity		
Hispanic or Latino	243 (18.6)	130 (19.6)
Not Hispanic or Latino	1059 (81.1)	533 (80.4)
Not reported	<1.0%	<1.0%
Comorbidities[d]		
Yes	262 (20.1)	133 (20.1)
No	1043 (79.9)	530 (79.9)

a. N = number of participants in the specified group from the evaluable efficacy population with no evidence of SARS CoV-2 infection prior to 7 days after Dose 2. This value is the denominator for the percentage calculations. Evaluable efficacy population included all eligible randomized participants who received all vaccination(s) as randomized within the predefined window, had no other important protocol deviations as determined by the clinician.
b. n = Number of participants with the specified characteristic.
c. Includes multiracial and not reported.
d. Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as participants who had at least 1 of the prespecified comorbidities based on MMWR 69(32);1081-1088 and/or obesity (BMI ≥95th percentile).

The descriptive vaccine efficacy results in children 5 through <12 years of age without evidence of prior SARS-CoV-2 infection are presented in Table 16. None of the cases accrued met criteria for severe COVID-19 or multisystem inflammatory syndrome in children (MIS-C). No cases of COVID-19 were observed in either the vaccine group or the placebo group in participants with evidence of prior SARS-CoV-2 infection.[82]

Table 16. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2: Without Evidence of Infection Prior to 7 Days After Dose 2 – Phase 2/3 – Children 5 Through <12 Years of Age Evaluable Efficacy Population[82]

First COVID-19 occurrence from 7 days after Dose 2 in children 5 through <12 years of age without evidence of prior SARS-CoV-2 infection*			
	TRADENAME 10 mcg/dose N[a]=1305 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=663 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)
Children 5 through 11 years of age	3 0.322 (1273)	16 0.159 (637)	90.7 (67.7, 98.3)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting).
* Participants who had no evidence of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
a. N = Number of participants in the specified group.

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b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1,000 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.

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

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

In Study 3, an analysis of SARS-CoV-2 50% neutralizing titers (NT50) 1 month after Dose 2 in a randomly selected subset of participants demonstrated effectiveness by immunobridging of immune responses comparing children 5 through <12 years of age in the Phase 2/3 part of Study 3 to participants 16 through 25 years of age in the Phase 2/3 part of Study 2 who had no serological or virological evidence of past SARSCoV-2 infection up to 1 month after Dose 2, meeting the prespecified immunobridging criteria for both the GMR and the seroresponse difference with seroresponse defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from baseline (before Dose 1).

The ratio of the SARS-CoV-2 NT50 in children 5 through <12 years of age to that of young adults 16 through 25 years of age was 1.04 (2-sided 95% CI: 0.93, 1.18), as presented in Table 17.

Table 17. Summary of Geometric Mean Ratio for 50% Neutralizing Titer – Comparison of Children 5 Through <12 Years of Age (Study 3) to Participants 16 Through 25 Years of Age (Study 2) – Participants Without* Evidence of Infection up to 1 Month After Dose 2 – Dose 2 Evaluable Immunogenicity Population[73]

		TRADENAME			
		10 mcg/Dose 5 Through <12 Years n^a=264	30 mcg/Dose 16 Through 25 Years n^a=253	5 Through <12 Years/ 16 Through 25 Years	
Assay	Time Point[b]	GMT[c] (95% CI[c])	GMT[c] (95% CI[c])	GMR[d] (95% CI[d])	Met Immunobridging Objective[e] (Y/N)
SARS-CoV-2 neutralization assay - NT50 (titer)[f]	1 month after Dose 2	1197.6 (1106.1, 1296.6)	1146.5 (1045.5, 1257.2)	1.04 (0.93, 1.18)	Y

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

* Participants who had no serological or virological evidence (up to 1 month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and 1 month after Dose 2, SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT (nasal swab) at any

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unscheduled visit up to 1 month after Dose 2 blood collection) and had no medical history of COVID-19 were included in the analysis.

a. n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
b. Protocol-specified timing for blood sample collection.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
d. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titers (Group 1[5 through <12 years of age] - Group 2 [16 through 25 years of age]) and the corresponding CI (based on the Student t distribution).
e. Immunobridging is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥0.8.
f. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, 99.2% of children 5 through <12 years of age and 99.2% of participants 16 through 25 years of age had a seroresponse from before vaccination to 1 month after Dose 2. The difference in proportions of participants who had seroresponse between the 2 age groups (children – young adult) was 0.0% (2-sided 95% CI: -2.0%, 2.2%), as presented in Table 18.

Table 18. Difference in Percentages of Participants With Seroresponse – Participants Without* Evidence of Infection up to 1 Month After Dose 2 – Immunobridging Subset – Phase 2/3 – Comparison of 5 Through <12 Years of Age to Study 2 Phase 2/3 16 Through 25 Years of Age – Evaluable Immunogenicity Population[73]

		TRADENAME			
		Study 3 10 mcg/Dose 5 Through <12 Years N[a]=264	Study 2 30 mcg/Dose 16 Through 25 Years N[a]=253	5 Through <12 Years / 16 Through 25 Years	
Assay	Time Point[b]	n[c] (%) (95% CI[d])	n[c] (%) (95% CI[d])	Difference %[e] (95% CI[f])	Met Immunobridging Objective[g] (Y/N)
SARS-CoV-2 neutralization assay - NT50 (titer)[h]	1 month after Dose 2	262 (99.2) (97.3, 99.9)	251 (99.2) (97.2, 99.9)	0.0 (-2.0, 2.2)	Y

Abbreviations: LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer 50; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result ≥4 × LLOQ is considered a seroresponse.

* Participants who had no serological or virological evidence (up to 1 month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and 1 month after Dose 2, SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT (nasal swab) at any unscheduled visit up to 1 month after Dose 2 blood collection) and had no medical history of COVID-19 were included in the analysis.

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a. N = number of participants with valid and determinate assay results both before vaccination and at 1 month after Dose 2. These values are the denominators for the percentage calculations.
b. Protocol-specified timing for blood sample collection.
c. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.
d. Exact 2-sided CI based on the Clopper and Pearson method.
e. Difference in proportions, expressed as a percentage (Group 1 [5 through <12 years of age] – Group 2 [16 through 25 years of age]).
f. 2-Sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
g. Immunobridging is declared if the lower bound of the 2-sided 95% CI for the difference in proportions is greater than -10.0%.
h. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

Efficacy and immunogenicity in individuals 6 months through <5 years of age – 3-dose primary course[86]

A descriptive efficacy analysis was performed across the combined population of participants 6 months through <5 years of age based on cases confirmed among 992 participants in the TRADENAME group and 464 participants in the placebo group who received all 3 doses of study intervention during the blinded follow-up period. The observed vaccine efficacy from at least 7 days after Dose 3 to the cutoff date (29 April 2022) was 80.3% (2-sided 95% CI: 13.9, 96.7) based on 3 cases in the TRADENAME group and 7 cases in the placebo group, adjusted for surveillance time (noting 2:1 randomization ratio).

Children 2 through 4 years of age – after 3 doses[86]

A descriptive efficacy analysis of Study 3 has been performed in participants 2 through 4 years of age. This analysis evaluated confirmed symptomatic COVID-19 cases accrued up to a data cutoff date of 29 April 2022.

Table 19 presents the specific demographic characteristics in participants 2 through 4 years of age who received 3 doses of TRADENAME (3 mcg modRNA) or placebo.

Table 19. Demographics Characteristics – Phase 2/3 – Participants 2 Through 4 Years of Age – Dose 3 All-Available Efficacy Population[99]

	TRADENAME 3 mcg/Dose (N[a]=606) n[b] (%)	**Placebo (N[a]=280) n[b] (%)**
Sex		
Male	290 (47.9)	124 (44.3)
Female	316 (52.1)	156 (55.7)

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	TRADENAME 3 mcg/Dose (N[a]=606) n[b] (%)	**Placebo (N[a]=280) n[b] (%)**
Age at Vaccination (years)		
Mean (SD)	2.9 (0.77)	2.9 (0.75)
Median	3.0	3.0
Min, max	(2, 4)	(2, 4)
Race		
White	455 (75.1)	219 (78.2)
Black or African American	29 (4.8)	13 (4.6)
American Indian or Alaska Native	0	2 (0.7)
Asian	64 (10.6)	26 (9.3)
Native Hawaiian or other Pacific Islander	1 (0.2)	0
Other[c]	57 (9.4)	20 (7.1)
Ethnicity		
Hispanic or Latino	77 (12.7)	36 (12.9)
Not Hispanic or Latino	528 (87.1)	244 (87.1)
Not reported	1 (0.2)	0
Comorbidities[d]		
Yes	71 (11.7)	42 (15.0)
No	535 (88.3)	238 (85.0)

Abbreviations: BMI = body mass, SD = standard deviation.

a. N = Number of participants in the specified group from the Dose 3 all-available efficacy population. This value is the denominator for the percentage calculations. Dose 3 all-available efficacy population included all randomized participants who received 3 doses of TRADENAME (3 mcg modRNA) or placebo.
b. n = Number of participants with the specified characteristic.
c. Includes multiracial and not reported.
d. Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as participants who had at least 1 of the prespecified comorbidities based on Morbidity and Mortality Weekly Report 69(32);1081-1088 and/or obesity (BMI ≥95th percentile).

The descriptive vaccine efficacy results after Dose 3 in participants 2 through 4 years of age are presented in Table 20.

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Table 20. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 3 - Phase 2/3 – Participants 2 Through 4 Years of Age – Dose 3 All-available Efficacy Population (Blinded Follow-up Period)[100]

	TRADENAME 3 mcg/Dose N[a]=606 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=280 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy (%) (95% CI[e])
First COVID-19 occurrence from 7 days after Dose 3	2 0.056 (481)	5 0.025 (209)	82.3 (-8.0, 98.3)

Abbreviation: VE = vaccine efficacy.

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; inability to eat/poor feeding).

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 3 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Two-sided 95% confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.

Additional evaluation of vaccine efficacy for cases confirmed at least 7 days after Dose 2 and before Dose 3 was performed. In the evaluable efficacy population in participants without prior evidence of SARS-CoV-2 infection before or during the vaccination regimen the observed vaccine efficacy from at least 7 days after Dose 2 and before Dose 3 was 35.9% (2-sided 95% CI: 11.0%, 53.7%). The vaccine efficacy in participants with or without prior evidence of SARS-CoV-2 infection before or during the vaccination regimen was similar.

Analysis of COVID-19 cases that excluded those involving coinfection with other respiratory pathogens did not meaningfully impact the estimated vaccine efficacy in this population.

Severe COVID-19 criteria (as described in the protocol, based on FDA definition and modified for children) were fulfilled for 7 cases (6 TRADENAME and 1 placebo) among participants 2 through 4 years of age, of which 5 of the 6 cases in the TRADENAME group fulfilled a single criterion of increased heart rate or respiratory rate and 1 case in the placebo group fulfilled a single criterion of decreased peripheral oxygen saturation (88% on room air). None of the cases accrued met criteria for multisystem inflammatory syndrome in children (MIS-C).

Immunogenicity analyses have been performed in the immunobridging subset of 143 Study 3 participants 2 through 4 years of age without evidence of infection up to 1 month after Dose 3 based on a data cutoff date of 29 April 2022.

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Table 21 presents the specific demographic characteristics in the studied evaluable immunogenicity population.

Table 21. Demographics Characteristics – Immunobridging Subset – Participants 2 Through 4 Years of Age (Study 3) and Participants 16 Through 25 Years of Age (Study 2) – Without Evidence of Infection -Evaluable Immunogenicity Population[101]

	TRADENAME 3 mcg/Dose 2 Through 4 Years of Age (N[a]=143) n[b] (%)	TRADENAME 30 mcg/Dose 16 Through 25 Years of Age (N[a]=170) n[b] (%)
Sex		
Male	63 (44.1)	79 (46.5)
Female	80 (55.9)	91 (53.5)
Age at Vaccination (years)		
Mean (SD)	2.7 (0.76)	21.2 (2.95)
Median	3.0	2.0
Min, max	(2, 4)	(16, 25)
Race		
White	99 (69.2)	130 (76.5)
Black or African American	8 (5.6)	15 (8.8)
American Indian or Alaska Native	0	3 (1.8)
Asian	16 (11.2)	13 (7.6)
Native Hawaiian or other Pacific Islander	0	1 (0.6)
Other[c]	20 (14.0)	8 (4.7)
Ethnicity		
Hispanic or Latino	16 (11.2)	51 (30.0)
Not Hispanic or Latino	126 (88.1)	119 (70.0)
Not reported	1 (0.7)	0

Note: Participants who had no serological or virological evidence (up to 1 month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at pre-Dose 1 and 1 month after Dose 2, SARS-CoV-2 not detected by NAAT [nasal swab] at pre-Dose 1 and pre-Dose 2, and negative NAAT [nasal swab] at any unscheduled visit up to 1 month after Dose 2 blood collection) and had no medical history of COVID-19 were included in the analysis.

a. N = Number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. Includes multiracial and not reported.

SARS-CoV-2 50% neutralizing antibody titers (NT50) were compared between an immunogenicity subset of Phase 2/3 participants 2 through 4 years of age from Study 3 at 1 month after the 3-dose primary course and a randomly selected subset from Study 2 (Phase 2/3) participants 16 through 25 years of age at 1 month after the 2-dose primary course, using a microneutralization assay against the reference strain (USA_WA1/2020). The primary

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immunobridging analyses compared the geometric mean titers (using a GMR) and the seroresponse (defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from before Dose 1) rates in the evaluable immunogenicity population of participants without evidence of prior SARS-CoV-2 infection up to 1 month after Dose 3 in participants 2 through 4 years of age and up to 1 month after Dose 2 in participants 16 through 25 years of age. The prespecified immunobridging criteria were met for both the GMR and the seroresponse difference (Table 22 and Table 23, respectively).

Table 22. SARS-CoV-2 GMTs (NT50) at 1 Month After Vaccination Course – Immunobridging Subset - Participants 2 Through 4 Years of Age (Study 3) 1 Month After Dose 3 and Participants 16 Through 25 Years of Age (Study 2) 1 Month After Dose 2 – Without Evidence of SARS-CoV-2 Infection – Evaluable Immunogenicity Population[102]

	TRADENAME		
	3 mcg/Dose 2 Through 4 Years of Age (1 month After Dose 3) n[a]=143	30 mcg/Dose 16 Through 25 Years of Age (1 Month After Dose 2) n[a]=170	GMR (95%CI) (2 Through 4 Years of Age/16 Through 25 Years of Age)[c,d]
Assay	GMT[b] (95% CI[b])	GMT[b] (95% CI[b])	
SARS-CoV-2 neutralization assay - NT50 (titer)[e]	1535.2 (1388.2, 1697.8)	1180.0 (1066.6, 1305.4)	1.30 (1.13, 1.50)

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Participants who had no serological or virological evidence [(up to 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3) blood sample collection)] of past SARS-CoV-2 infection [i.e., N-binding antibody [serum] negative at Dose 1, Dose 3 (Study 3) and 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3), SARS-CoV-2 not detected by NAAT [nasal swab] at Dose 1, Dose 2, and Dose 3 (Study 3) study visits, and negative NAAT [nasal swab] at any unscheduled visit up to 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3) blood collection] and had no medical history of COVID-19 were included in the analysis.

a. n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
b. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
c. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titers (2 to 4 years of age minus 16 to 25 years of age) and the corresponding CI (based on the Student t distribution).
d. Immunobridging is declared if the lower bound of the 2-sided 95% CI for the GMR ratio is greater than 0.67 and the point estimate of the GMR is ≥0.8.
e. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

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Table 23. Difference in Percentages of Participants With Seroresponse at 1 Month After Vaccination Course – Immunobridging Subset –Participants 2 Through 4 Years of Age (Study 3) 1 Month After Dose 3 and Participants 16 Through 25 Years of Age (Study 2) 1 Month After Dose 2 Without Evidence of Infection – Evaluable Immunogenicity Population[103]

	TRADENAME		
	3 mcg/Dose 2 Through 4 Years of Age (1 Month After Dose 3) N[a]=141	30 mcg/Dose 16 Through 25 Years of Age (1 Month After Dose 2) N[a]=170	Difference in Seroresponse Rates %[d] (95% CI[e]) (2 Through 4 Years of age Minus 16 Through 25 Years of Age)[f]
Assay	n[b] (%) (95% CI[c])	n[b] (%) (95% CI[c])	
SARS-CoV-2 neutralization assay - NT50 (titer)[g]	141 (100.0) (97.4, 100.0)	168 (98.8) (95.8, 99.9)	1.2 (-1.5, 4.2)

Abbreviations: LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer 50; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result ≥4 × LLOQ is considered a seroresponse.

Note: Participants who had no serological or virological evidence (up to 1 month after Dose 2 [(Study 2) or 1 month after Dose 3 (Study 3) blood sample collection)[of past SARS-CoV-2 infection [i.e., N-binding antibody [serum] negative at pre-Dose 1, pre-Dose 3 (Study 3) and 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3), SARS-CoV-2 not detected by NAAT [nasal swab] at pre-Dose 1, pre-Dose 2, and pre-Dose 3 (Study 3) study visits, and negative NAAT [nasal swab] at any unscheduled visit up to 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3) blood collection] and had no medical history of COVID-19 were included in the analysis.

a. N = Number of participants with valid and determinate assay results both before vaccination and at 1 month after Dose 2. These values are the denominators for the percentage calculations.
b. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.
c. Exact 2-sided CI based on the Clopper and Pearson method.
d. Difference in proportions, expressed as a percentage (2 through 4 years of age minus 16 through 25 years of age).
e. 2-sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
f. Immunobridging is declared if the lower bound of the 2-sided 95% CI for the difference in proportions is greater than -10.0% provided that the immunobridging criteria based on GMR were met.
g. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

Using a non-validated fluorescence focus reduction neutralization test assay against the Omicron variant of SARS-CoV-2 (BA.1), the NT50 GMT at 1 month after Dose 3 among a subset of 34 study participants without evidence of prior SARS-CoV-2 infection (82.5 [2-sided 95% CI: 55.4, 122.9]) was increased compared to the NT50 GMT before Dose 3 (14.0 [2-sided 95% CI: 10.6, 18.5]).

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An additional descriptive immunogenicity analysis was performed for participants 2 through 4 years of age who received a 3-dose course of TRADENAME in Study 3 (Phase 2/3), compared with a subset of participants 18 through 50 years of age in Study C4591017 (Phase 3) who had received a 2-dose primary course followed by a booster dose of TRADENAME 30 mcg. The comparator group (participants 18 through 50 years of age) in this analysis had a similar interval between TRADENAME Dose 2 and Dose 3 (median 13.0 weeks) as the participants 2 to 4 years of age (median 10.6 weeks). Among 34 participants 2 through 4 years of age without evidence of prior SARS-CoV-2 infection who received 3 doses of TRADENAME 3 mcg, neutralizing GMTs were 114.3 at 1-month post-Dose 3. Among 27 participants 18 through 50 years of age without evidence of prior SARS-CoV-2 infection who received 3 doses of TRADENAME 30 mcg, Omicron neutralizing GMTs were 164.2 at 1-month post-Dose 3.

Infants 6 through 23 months of age – after 3 doses[86]

A descriptive efficacy analysis of Study 3 has been performed in participants 6 through 23 months of age. This analysis evaluated confirmed symptomatic COVID-19 cases accrued up to a data cutoff date of 29 April 2022.

Table 24 presents the specific demographic characteristics in participants 6 through 23 months of age who received 3 doses of TRADENAME (3 mcg modRNA) or placebo.

Table 24. Demographics Characteristics – Phase 2/3 – Participants 6 Through 23 Months of Age – Dose 3 All-Available Efficacy Population[104]

	TRADENAME 3 mcg/Dose (N[a]=386) n[b] (%)	**Placebo (N[a]=184) n[b] (%)**
Sex		
Male	189 (49.0)	79 (42.9)
Female	197 (51.0)	105 (57.1)
Age at Vaccination (months)		
Mean (SD)	15.4 (4.92)	15.2 (5.14)
Median	16.0	15.5
Min, max	(6, 23)	(6, 23)
Race		
White	290 (75.1)	136 (73.9)
Black or African American	10 (2.6)	11 (6.0)
American Indian or Alaska Native	1 (0.3)	0
Asian	42 (10.9)	17 (9.2)
Other[c]	43 (11.1)	20 (10.9)
Ethnicity		
Hispanic or Latino	40 (10.4)	13 (7.1)
Not Hispanic or Latino	344 (89.1)	169 (91.8)
Not reported	2 (0.5)	2 (1.1)

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	TRADENAME 3 mcg/Dose (N[a]=386) n[b] (%)	Placebo (N[a]=184) n[b] (%)
Comorbidities[d]		
Yes	17 (4.4)	9 (4.9)
No	369 (95.6)	175 (95.1)

Abbreviation: SD = standard deviation.
a. N = Number of participants in the specified group from the Dose 3 all-available efficacy population. This value is the denominator for the percentage calculations. Dose 3 all-available efficacy population included all randomized participants who received 3 doses of TRADENAME (3 mcg modRNA) or placebo.
b. n = Number of participants with the specified characteristic.
c. Includes multiracial and not reported.
d. Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as participants who had at least 1 of the prespecified comorbidities based on Morbidity and Mortality Weekly Report 69(32);1081-1088.

The descriptive vaccine efficacy results after dose 3 in participants 6 through 23 months of age are presented in Table 25.

Table 25. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 3 – Phase 2/3 – Participants 6 Through 23 Months of Age – Dose 3 All-available Efficacy Population (Blinded Follow-up Period)[105]

	TRADENAME 3 mcg/Dose N[a]=386 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=184 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy (%) (95% CI[e])
First COVID-19 occurrence from 7 days after Dose 3	1 0.030 (277)	2 0.015 (139)	75.5 (-370.1, 99.6)

Abbreviation: VE = vaccine efficacy.
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; inability to eat/poor feeding).
a. N = Number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1,000 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 3 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Two-sided 95% confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.

Additional evaluation of vaccine efficacy for cases confirmed at least 7 days after Dose 2 and before Dose 3 was performed. In the evaluable efficacy population in participants without prior evidence of SARS-CoV-2 infection before or during the vaccination regimen the observed

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vaccine efficacy from at least 7 days after Dose 2 and before Dose 3 was 16.1% (2-sided 95% CI: -24.9%, 43.1%). The vaccine efficacy in participants with or without prior evidence of SARS-CoV-2 infection before or during the vaccination regimen was similar.

Analysis of COVID-19 cases that excluded those involving coinfection with other respiratory pathogens did not meaningfully impact the estimated vaccine efficacy in this population.

One participant in the placebo group, had confirmed COVID-19 which met a single severe case criterion described in the protocol (increased heart rate [172 bpm]). None of the cases accrued met criteria for multisystem inflammatory syndrome in children (MIS-C).

Immunogenicity analyses have been performed in the immunobridging subset of 82 Study 3 participants 6 through 23 months of age without evidence of infection up to 1 month after Dose 3 based on a data cutoff date of 29 April 2022.

Table 26 presents the specific demographic characteristics in the studied evaluable immunogenicity population.

Table 26. Demographics Characteristics – Immunobridging Subset – Participants 6 Through 23 Months of Age (Study 3) and Participants 16 Through 25 Years of Age (Study 2) – Without Evidence of Infection -Evaluable Immunogenicity Population[106]

	TRADENAME 3 mcg/Dose 6 Through 23 Months of Age (N[a]=82) n[b] (%)	TRADENAME 30 mcg/Dose 16 Through 25 Years of Age (N[a]=170) n[b] (%)
Sex		
Male	51 (62.2)	79 (46.5)
Female	31 (37.8)	91 (53.5)
Age at Vaccination (years)		
Mean (SD)	15.7 (4.84)	21.2 (2.95)
Median	16.0	2.0
Min, max	(6, 23)	(16, 25)
Race		
White	59 (72.0)	130 (76.5)
Black or African American	1 (1.2)	15 (8.8)
American Indian or Alaska Native	1 (1.2)	3 (1.8)
Asian	11 (13.4)	13 (7.6)
Native Hawaiian or other Pacific Islander	0	1 (0.6)
Other[c]	10 (12.2)	8 (4.7)

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	TRADENAME 3 mcg/Dose 6 Through 23 Months of Age (N[a]=82) n[b] (%)	TRADENAME 30 mcg/Dose 16 Through 25 Years of Age (N[a]=170) n[b] (%)
Ethnicity		
Hispanic or Latino	13 (15.9)	51 (30.0)
Not Hispanic or Latino	69 (84.1)	119 (70.0)

Note: Participants who had no serological or virological evidence (up to 1 month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at pre-Dose 1 and 1 month after Dose 2, SARS-CoV-2 not detected by NAAT [nasal swab] at pre-Dose 1 and pre-Dose 2, and negative NAAT [nasal swab] at any unscheduled visit up to 1 month after Dose 2 blood collection) and had no medical history of COVID-19 were included in the analysis.

a. N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. Includes multiracial and not reported.

SARS-CoV-2 50% neutralizing antibody titers (NT50) 1 month after the vaccination course were compared between an immunogenicity subset of Phase 2/3 participants 6 through 23 months of age from Study 3 and a randomly selected subset from Study 2 (Phase 2/3) participants 16 through 25 years of age, using a microneutralization assay against the reference strain (USA_WA1/2020). The primary immunobridging analyses compared the geometric mean titers (using a GMR) and the seroresponse (defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from before Dose 1) rates in the evaluable immunogenicity population of participants without evidence of prior SARS-CoV-2 infection up to 1 month after Dose 3 in participants 6 through 23 months of age and up to 1 month after Dose 2 in participants 16 through 25 years of age. The prespecified immunobridging criteria were met for both the GMR and the seroresponse difference (Table 27 and Table 28, respectively).

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Table 27. SARS-CoV-2 GMTs (NT50) at 1 Month After Vaccination Course – Immunobridging Subset - Participants 6 Through 23 Months of Age (Study 3) 1 Month After Dose 3 and Participants 16 rough 25 Years of Age (Study 2) 1 Month After Dose 2 – Without Evidence of SARS-CoV-2 – Evaluable Immunogenicity Population[107]

	TRADENAME		
	3 mcg/Dose 6 Through 23 Months of Age (1 Month After Dose 3) n[a]=82	30 mcg/Dose 16 Through 25 Years of Age (1 Month After Dose 2) n[a]=170	GMR (95%CI) (6 Through 23 Months of Age/16 Through 25 Years of Age)[c,d]
Assay	GMT[b] (95% CI[b])	GMT[b] (95% CI[b])	
SARS-CoV-2 neutralization assay - NT50 (titer)[e]	1406.5 (1211.3, 1633.1)	1180.0 (1066.6, 1305.4)	1.19 (1.00, 1.42)

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Participants who had no serological or virological evidence [(up to 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3) blood sample collection)] of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Dose 1, Dose 3 (Study 3) and 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3), SARS-CoV-2 not detected by NAAT [nasal swab] at Dose 1, Dose 2, and Dose 3 (Study 3) study visits, and negative NAAT [nasal swab] at any unscheduled visit up to 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3) blood collection)] and had no medical history of COVID-19 were included in the analysis.

a. n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
b. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
c. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titers (6 through 23 months of age minus 16 through 25 years of age) and the corresponding CI (based on the Student t distribution).
d. Immunobridging is declared if the lower bound of the 2-sided 95% CI for the GMR ratio is greater than 0.67 and the point estimate of the GMR is ≥0.8.
e. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

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Table 28. Difference in Percentages of Participants With Seroresponse at 1 Month After Vaccination Course – Immunobridging Subset – Participants 6 Through 23 Months of Age (Study 3) 1 Month After Dose 3 and Participants 16 Through 25 Years of Age (Study 2) to 1 Month After Dose 2 Without Evidence of Infection – Evaluable Immunogenicity Population[108]

	TRADENAME		
	3 mcg/Dose 6 Through 23 Months of Age (1 Month After Dose 3) N[a]=80	30 mcg/Dose 16 Through 25 Years of Age (1 Month After Dose 2) N[a]=170	Difference in Seroresponse Rates %[d] (95% CI[e]) (6 Through 23 Months of Age Minus 16 Through 25 Years of Age)[f]
Assay	n[b] (%) (95% CI[c])	n[b] (%) (95% CI[c])	
SARS-CoV-2 neutralization assay - NT50 (titer)[g]	80 (100.0) (95.5, 100.0)	168 (98.8) (95.8, 99.9)	1.2 (-3.4, 4.2,)

Abbreviations: LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer 50; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result ≥4 × LLOQ is considered a seroresponse.

Note: Participants who had no serological or virological evidence [(up to 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3) blood sample collection) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at pre-Dose 1, Dose 3 (Study 3) and 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3), SARS-CoV-2 not detected by NAAT [nasal swab] at pre-Dose 1, pre-Dose 2, and pre-Dose 3 (Study 3) study visits, and negative NAAT [nasal swab] at any unscheduled visit up to 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3) blood collection)] and had no medical history of COVID-19 were included in the analysis.

a. N = Number of participants with valid and determinate assay results both before vaccination and at 1 month after Dose 2. These values are the denominators for the percentage calculations.
b. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.
c. Exact 2-sided CI based on the Clopper and Pearson method.
d. Difference in proportions, expressed as a percentage (6 through 23 months of age minus 16 through 25 years of age).
e. 2-sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
f. Immunobridging is declared if the lower bound of the 2-sided 95% CI for the difference in proportions is greater than -10.0% provided that the immunobridging criteria based on GMR were met.
g. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

Using a non-validated fluorescence focus reduction neutralization test assay against the Omicron variant of SARS-CoV-2 (BA.1), the NT50 GMT at 1 month after Dose 3 among a subset of 32 study participants without evidence of prior SARS-CoV-2 infection (127.5 [2-sided 95% CI: 90.2, 180.1]) was increased compared to the NT50 GMT before Dose 3 (16.3 [2-sided 95% CI: 12.8, 20.8]).

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An additional descriptive immunogenicity analysis was performed for participants 6 through 23 months of age who received a 3-dose course of TRADENAME in Study 3 (Phase 2/3), compared with a subset of participants 18 through 50 years of age in Phase 3 Study C4591017 who had received a 2-dose primary course followed by a booster dose of TRADENAME 30 mcg. The comparator group (participants 18 through 50 years of age) in this analysis had a similar interval between TRADENAME Dose 2 and Dose 3 (median 13.0 weeks) as the participants 6 through 23 months of age (median 12.9 weeks). Among 32 participants 6 through 23 months of age without evidence of prior SARS-CoV-2 infection who received 3 doses of TRADENAME 3 mcg, Omicron neutralizing GMTs were 128.8 at 1-month post-Dose 3. Among 27 participants 18 through 50 years of age without evidence of prior SARS-CoV-2 infection who received 3 doses of TRADENAME 30 mcg, Omicron neutralizing GMTs were 164.2 at 1-month post-Dose 3.

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

Effectiveness of a booster dose of TRADENAME was demonstrated by evaluating noninferiority immune responses of SARS-CoV-2 NT50 1 month after a booster dose. In Study 2, an analysis of SARS-CoV-2 NT50 demonstrated non-inferior immune responses 1 month after a booster dose compared to 1 month after Dose 2 in participants at least 18 through 55 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the booster dose, based on prespecified noninferiority criteria for both GMR and difference in seroresponse rates. Seroresponse for a participant was defined as achieving a ≥4-fold rise from baseline (before Dose 1) in NT50 (Table 29 and Table 30).

The SARS-CoV-2 NT50 GMR of 1 month after the booster dose to 1 month after Dose 2 was 3.26 (2-sided 97.5% CI: 2.76, 3.86), which met the noninferiority criteria for GMR (lower bound of the 2-sided 97.5% CI >0.67 and point estimate of the GMR ≥0.8).

A high proportion of participants (99.5%) had seroresponse 1 month after Dose 3 compared with 95.0% 1 month after Dose 2. The difference in proportions of participants with a seroresponse 1 month after the booster dose (Dose 3) and 1 month after Dose 2 (Dose 3 minus Dose 2) was 1.5% (2-sided 97.5% CI: 1.0%, 7.9%), which met the 10% noninferiority criterion (i.e., lower bound of the 2-sided 97.5% CI >10%).

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Table 29. Summary of Geometric Mean Ratio for 50% Neutralizing Titer – Comparison of 1 Month After Booster Dose to 1 Month After Dose 2 – Participants Without Evidence of Infection up to 1 Month After Booster Dose* – Booster Dose Evaluable Immunogenicity Population±,71,109,110

		TRADENAME Sampling Time Point			
		1 Month After Booster Dose	1 Month After Dose 2	1 Month After Booster Dose - 1 Month After Dose 2	Met Noninferiority Objective[d] (Y/N)
Assay	n[a]	GMT[b] (95% CI[b])	GMT[b] (95% CI[b])	GMR[c] (97.5% CI[c])	
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)[e]	212	2466.0 (2202.6, 2760.8)	755.7 (663.1, 861.2)	3.26 (2.76, 3.86)	Y

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

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

± All eligible participants who had received 2 doses of TRADENAME as initially randomized, with Dose 2 received within the predefined window (within 19 to 42 days after Dose 1), received a booster dose of TRADENAME, had at least 1 valid and determinate immunogenicity result after booster dose from a blood collection within an appropriate window (within 28 to 42 days after the booster dose), and had no other important protocol deviations as determined by the clinician.

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

b. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.

c. GMRs and 2-sided 97.5% CIs were calculated by exponentiating the mean differences in the logarithms of the assay and the corresponding CIs (based on the Student t distribution).

d. Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the GMR is >0.67 and the point estimate of the GMR is ≥0.80.

e. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

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Table 30. Percentage Difference of Participants Achieving Seroresponse – Comparison of 1 Month After Booster Dose to 1 Month After Dose 2 – Phase 3 – Participants Without Evidence of Infection up to 1 Month After Booster Dose* – Booster Dose Evaluable Immunogenicity Population±,71,110,111

		TRADENAME Sampling Time Point		Difference (1 Month After Booster Dose - 1 Month After Dose 2)	Met Noninferiority Objective[f] (Y/N)
		1 Month After Booster Dose	1 Month After Dose 2		
Assay	N[a]	n[b] % (95% CI[c])	n[b] % (95% CI[c])	%[d] (97.5% CI[e])	
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)[g]	200	199 99.5 (97.2, 100.0)	190 95.0 (91.0, 97.6)	4.5 (1.0, 7.9)	Y

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

Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result ≥4 × LLOQ is considered a seroresponse.

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

± All eligible participants who had received 2 doses of TRADENAME as initially randomized, with Dose 2 received within the predefined window (within 19 to 42 days after Dose 1), received a booster dose of TRADENAME, had at least 1 valid and determinate immunogenicity result after booster dose from a blood collection within an appropriate window (within 28 to 42 days after the booster dose), and had no other important protocol deviations as determined by the clinician.

a. N = number of participants with valid and determinate assay results for the specified assay at baseline, 1 month after Dose 2 and 1 month after the booster dose within specified window. These values are the denominators for the percentage calculations.

b. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.

c. Exact 2-sided CI based on the Clopper and Pearson method.

d. Difference in proportions, expressed as a percentage (1 month after booster dose – 1 month after Dose 2).

e. Adjusted Wald 2-sided CI for the difference in proportions, expressed as a percentage.

f. Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the percentage difference is >-10%.

g. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

Relative vaccine efficacy in participants 16 years of age and older – after booster dose[80,112,113]

An interim efficacy analysis of Study 4, a placebo-controlled booster study, was performed in approximately 10,000 participants 16 years of age and older who were recruited from Study 2, evaluated confirmed COVID-19 cases accrued from at least 7 days after booster vaccination up to a data cut-off date of 8 February 2022 (a period when Delta and then Omicron was the predominant variant), which represents a median of 2.8 months (range 0.3 to 7.5 months) post-booster follow-up. Vaccine efficacy of the TRADENAME booster dose after the primary series relative to the placebo booster group who only received the primary series dose was

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assessed. The relative vaccine efficacy information for participants 16 years of age and older is presented in Table 31.

Table 31. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Booster Vaccination – Participants 16 Years of Age and Older Without Evidence of Infection and Participants With or Without Evidence of Infection Prior to 7 Days After Booster Vaccination – Evaluable Efficacy Population[80,114,115]

First COVID-19 occurrence from 7 days after booster dose in participants without evidence of prior SARS-CoV-2 infection*			
	TRADENAME N[a]=4689 Cases n1[b] Surveillance Time[c] (n2[d])	**Placebo N[a]=4664 Cases n1[b] Surveillance Time[c] (n2[d])**	**Relative Vaccine Efficacy[e] % (95% CI[f])**
First COVID-19 occurrence from 7 days after booster vaccination	63 1.098 (4639)	148 0.932 (4601)	63.9 (51.1, 73.5)
First COVID-19 occurrence from 7 days after booster dose in participants with or without evidence of prior SARS-CoV-2 infection			
	TRADENAME N[a]=4997 Cases n1[b] Surveillance Time[c] (n2[d])	**Placebo N[a]=4942 Cases n1[b] Surveillance Time[c] (n2[d])**	**Relative Vaccine Efficacy[e] % (95% CI[f])**
First COVID-19 occurrence from 7 days after booster vaccination	67 1.179 (4903)	150 0.989 (4846)	62.4 (49.5, 72.2)

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 serological or virological evidence (prior to 7 days after receipt of the booster vaccination) 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 Visit 1, and had a negative NAAT [nasal swab] at any unscheduled visit prior to 7 days after booster vaccination) 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 the booster vaccination to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Relative vaccine efficacy of the TRADENAME booster group relative to the placebo group (non-booster).
f. Two-sided confidence interval (CI) for relative vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.

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Immunogenicity in children 5 through <12 years of age – after booster dose[84]

Effectiveness of a booster dose of TRADENAME was based on an assessment of NT50 against the reference strain of SARS-CoV-2 (USA_WA1/2020). Analyses of NT50 1 month after the booster dose compared to before the booster dose (Dose 3) demonstrated a substantial increase in GMTs in individuals 5 through <12 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the booster dose. This analysis is summarized in Table 32.

Table 32. Summary of Geometric Mean Titers – NT50 – Participants Without Evidence of Infection – Phase 2/3 – Immunogenicity Set – 5 Through <12 Years of Age – Evaluable Immunogenicity Population

		TRADENAME 10 mcg/Dose					
		3-Dose Set		2-Dose Set		Total	
Assay	Dose/ Sampling Time Point[a]	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])
SARS-CoV-2 neutralization assay - NT50 (titer)	1 month Prevax	79	20.5 (20.5, 20.5)	67	20.5 (20.5, 20.5)	146	20.5 (20.5, 20.5)
	1 month after Dose 2	29	1659.4 (1385.1, 1988.0)	67	1110.7 (965.3, 1278.1)	96	1253.9 (1116.0, 1408.9)
	3 months Prevax	67	271.0 (229.1, 320.6)	-	-	67	271.0 (229.1, 320.6)
	1 month after Dose 3	67	2720.9 (2280.1, 3247.0)	-	-	67	2720.9 (2280.1, 3247.0)

Abbreviations: CI = confidence interval; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer; Prevax = before vaccination; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Three-dose immunogenicity set included the first 130 participants who received Dose 3 and completed 1-month post–Dose 3 visit prior to March 15, 2022. Among those, 30 had blood sample collection at 1-month post-Dose 2. Two-dose immunogenicity set included an extra 67 participants randomly selected from previous Dose-2 evaluable immunogenicity population and without evidence of infection up to 1-month post–Dose 2 subset used for 2-dose immunobridging analysis.
Note: Participants included in this analysis had no serological or virological evidence of past SARS-CoV-2 infection up to the 1-month post–Dose 2 (for 1-month post–Dose 2 time point) or 1-month post–Dose 3 (for pre–Dose 3 and 1-month post–Dose 3 time point) study blood sample collection. Having no evidence of past SARS-CoV-2 infection up to 1-month post–Dose 2 was defined as having a negative N-binding antibody (serum) result at the Dose 1 and 1-month post–Dose 2 study visits; a negative NAAT (nasal swab) result at the Dose 1 and Dose 2 study visits and any unscheduled visit prior to the 1-month post–Dose 2 blood sample collection; and no medical history of COVID-19. Having no evidence of past SARS-CoV-2 infection up to 1-month post-Dose 3 was defined as having a negative N-binding antibody (serum) result at the Dose 1, 1-month post–Dose 2 (if available), Dose 3, and 1-month post–Dose 3 study visits; a negative NAAT (nasal swab) result at the Dose 1, Dose 2, and Dose 3 study visits and any unscheduled visit prior to the 1-month post–Dose 3 blood sample collection; and no medical history of COVID-19.

a. Protocol-specified timing for blood sample collection.
b. n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.

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c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.

Immunogenicity in children 5 through <12 years of age on the Omicron variant – after booster dose[84]

The neutralizing GMTs against both the Omicron variant and reference strain were substantially increased after booster vaccination compared with after the 2-dose primary series. At 1-month post-Dose 2, the observed neutralizing GMTs for the Omicron variant and reference strain were 27.6 and 323.8, respectively. At 1-month post-Dose 3, the observed neutralizing GMTs for the Omicron variant and reference strain were 614.4 and 1702.8, respectively (see Table 33).

For the Omicron variant, neutralizing titers after booster vaccination (1-month post-Dose 3) increased 22-fold over those after the 2-dose primary series (1-month post-Dose 2). For the reference strain, the increase after the booster relative to the primary series was 5.3-fold.

Table 33. Summary of Geometric Mean Titers – Omicron-Neutralization Subset – Participants Without Evidence of Infection – Phase 2/3 – Immunogenicity Set – 5 Through <12 Years of Age – Evaluable Immunogenicity Population

		TRADENAME 10 mcg/Dose	
		Vaccine Group (as Randomized)	
Assay	Time Point[b]	n[b]	GMT[c] (95% CI[c])
SARS-COV-2 FFRNT- B.1.1.529 strain (Omicron) - NT50 (titer)	1 month after Dose 2	29	27.6 (22.1, 34.5)
	1 month after Dose 3	17	614.4 (410.7, 919.2)
SARS-CoV-2 FFRNT- reference strain - NT50 (titer)	1 month after Dose 2	29	323.8 (267.5, 392.1)
	1 month after Dose 3	17	1702.8 (1282.6, 2260.7)

Abbreviations: CI = confidence interval; FFRNT = fluorescence focus reduction neutralization test; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Participants included in this analysis had no serological or virological evidence of past SARS-CoV-2 infection up to the 1-month post–Dose 2 (for 1-month post–Dose 2 time point) or 1-month post–Dose 3 (for 1-month post–Dose 3 time point) study blood sample collection. Having no evidence of past SARS-CoV-2 infection up to 1-month post–Dose 2 was defined as having a negative N-binding antibody (serum) result at the Dose 1 and 1-month post–Dose 2 study visits; a negative NAAT (nasal swab) result at the Dose 1 and Dose 2 study visits and any unscheduled visit prior to the 1-month post–Dose 2 blood sample collection; and no medical history of COVID-19. Having no evidence of past SARS-CoV-2 infection up to 1-month post–Dose 3 was defined as having a negative N-binding antibody (serum) result at the Dose 1, 1-month post–Dose 2 (if available), Dose 3, and 1-month post–Dose 3 study visits; a negative NAAT (nasal swab) result at the Dose 1, Dose 2, and Dose 3 study visits and any unscheduled visit prior to the 1-month post–Dose 3 blood sample collection; and no medical history of COVID-19.

a. Protocol-specified timing for blood sample collection.

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b. n = Number of participants with valid and determinate assay results for the specified assays at the given dose/sampling time point.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.

Omicron-adapted TRADENAME

The efficacy of a booster dose of TRADENAME (Bivalent) is inferred from clinical data from the studies of a booster dose of an Omicron BA.1 adapted vaccine.

Immunogenicity in participants greater than 55 years of age – after a booster dose of TRADENAME (Bivalent, Original/Omicron BA.1) (fourth dose)

In an analysis of a subset from Study 4 (Substudy E), 610 adults greater than 55 years of age who had completed a series of 3 doses of TRADENAME received 1 of the following as a booster dose (fourth dose): TRADENAME (30 mcg) or TRADENAME (Bivalent, Original/Omicron BA.1) 15/15 mcg.[140] GMRs and seroresponse rates were evaluated at 1 month after TRADENAME (Bivalent, Original/Omicron BA.1)15/15 mcg booster vaccination.[141] TRADENAME (Bivalent, Original/Omicron BA.1) 15/15 mcg booster dose was administered 4.7 to 11.5 months (median 6.3 months) after the third dose.[140]

The primary objective of the analysis was to assess superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rate of the anti-Omicron immune response induced by a dose of TRADENAME (Bivalent, Original/Omicron BA.1) 15/15 mcg relative to the response elicited by a dose of TRADENAME (30 mcg) given as a fourth dose in TRADENAME-experienced participants greater than 55 years of age.

Superiority of TRADENAME (Bivalent, Original/Omicron BA.1) 15/15 mcg to TRADENAME (30 mcg) was met, as the lower bound of the 2-sided 95% CI for GMR was >1 (Table 34).[142]

The difference in proportions of participants who achieved seroresponse between the Omicron BA.1 (15/15 mcg) group and TRADENAME (30 mcg) group was 14.6 (2-sided 95% CI: 4.0, 24.9). Noninferiority was met, as the lower limit of the 2-sided 95% CI for the difference in percentages of participants with seroresponse was >-5% (Table 35).[143,154]

Table 34: Substudy E - Geometric Mean Ratios for Between Vaccine Group Comparison – Participants Without Evidence of Infection Up to 1 Month after Dose 4 – Expanded Cohort – Immunogenicity Subset – Participants Greater Than 55 Years of Age – Evaluable Immunogenicity Population[144]

Assay	Vaccine Group (as randomized)	Sampling Time Point[a]	N[b]	GMT (95% CI[c])	GMR (95% CI[d])
SARS-CoV-2 neutralization assay - Omicron BA.1 - NT50 (titer)	TRADENAME (30 mcg)	1 month	163	455.8 (365.9, 567.6)	
	TRADENAME(Bivalent) BA.1 (15/15 mcg)	1 month	178	711.0 (588.3, 859.2)	1.56 (1.17, 2.08)

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Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Immunogenicity subset = a random sample of 230 participants in each vaccine group selected from the expanded cohort.
Note: Participants who had no serological or virological evidence (prior to the 1-month post–study vaccination blood sample collection) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] result negative at the study vaccination and the 1-month post–study vaccination visits, negative NAAT [nasal swab] result at the study vaccination visit, and any unscheduled visit prior to the 1-month post–study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.
a. Protocol-specified timing for blood sample collection.
b. n = number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
d. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titers (vaccine group in the corresponding row - Comirnaty [30 mcg]) and the corresponding CI (based on the Student t distribution).

Table 35: Substudy E - Number (%) of Participants Achieving Seroresponse – Participants Without Evidence of Infection Up to 1 Month after Dose 4 – Expanded Cohort – Immunogenicity Subset – Participants Greater Than 55 Years of Age – Evaluable Immunogenicity Population[145]

Assay	Vaccine Group (as randomized)	Sampling Time Point[a]	N[b]	n[c] (%) (95% CI[d])	Difference %[e] (95% CI[f])
SARS-CoV-2 neutralization assay - Omicron BA.1 - NT50 (titer)	TRADENAME (30 mcg)	1 month	149	85 (57.0) (48.7, 65.1)	
	TRADENAME (Bivalent BA.1) (15/15 mcg)	1 month	169	121 (71.6) (64.2, 78.3)	14.6 (4.0, 24.9)

Abbreviations: LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Immunogenicity subset = a random sample of 230 participants in each vaccine group selected from the expanded cohort.
Note: Seroresponse is defined as achieving ≥4-fold rise from baseline (before the study vaccination). If the baseline measurement is below the LLOQ, the postvaccination measure of ≥4 × LLOQ is considered a seroresponse.
Note: Participants who had no serological or virological evidence (prior to the 1-month post–study vaccination blood sample collection) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] result negative at the study vaccination and the 1-month post–study vaccination visits, negative NAAT [nasal swab] result at the study vaccination visit, and any unscheduled visit prior to the 1-month post–study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.
a. Protocol-specified timing for blood sample collection.
b. N = Number of participants with valid and determinate assay results for the specified assay at both the pre-vaccination time point and the given sampling time point. This value is the denominator for the percentage calculation.
c. n = Number of participants with seroresponse at 1 month after vaccination for the given assay.
d. Exact 2-sided CI based on the Clopper and Pearson method.
e. Difference in proportions, expressed as a percentage (vaccine group in the corresponding row - Comirnaty [30 mcg]).
f. Two-sided CI based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.

Immunogenicity in participants 18 to ≤55 years of age – after a booster dose of TRADENAME or monovalent Omicron BA.1 (fourth dose)

In Substudy D [a subset from Study 2 (Phase 3) and Study 4 (Phase 3)], 640 participants 18 to ≤55 years of age who had completed 3 doses of TRADENAME received 1 of the following as a booster (fourth dose):[146,147] TRADENAME (30 mcg) or monovalent Omicron BA.1 90 to 180 days after receiving Dose 3.[147]

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In the primary immunogenicity subset of participants without prior evidence of infection up to 1 month after Dose 4, the ratio of GMTs for the monovalent Omicron BA.1 group to the TRADENAME group GMR was 1.75 (2-sided 95% CI: 1.39, 2.22) (Table 36).[148]

The lower bound of the 2-sided 95% CI for GMR was >1, which meets the prespecified simple superiority criterion. Therefore, superiority of monovalent Omicron BA.1 to TRADENAME for the Omicron variant was achieved based on the GMR at 1 month after Dose 4.[148]

The difference in proportions of participants who achieved seroresponse between the monovalent Omicron BA.1 group and TRADENAME group was 23.0% (2-sided 95% CI: 11.1, 34.3)[149] (Table 37), the noninferiority criterion (lower bound of the 2-sided 95% CI >-5)[150] was achieved.

Table 36: Substudy D – Geometric Mean Ratios for Between Vaccine Group Comparison - Cohort 2 - Primary Immunogenicity Subset - Participants Without Evidence of Infection Up to 1 Month After Dose 4 - Evaluable Immunogenicity Population[151]

		Vaccine Group (as randomized)				
		Monovalent Omicron BA.1 (30 mcg)		TRADENAME (30 mcg)		Monovalent Omicron BA.1 / TRADENAME
Assay	Dose/ Sampling Time Point[a]	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])	GMR[d] (95% CI)[d]
SARS-CoV-2 neutralization assay - Omicron BA.1 - NT50 (titer)	1/1 month	132	1929.2 (1631.5, 2281.1)	141	1099.6 (932.0, 1297.4)	1.75 (1.39, 2.22)

Abbreviations: GMT = geometric mean titer; GMR = geometric mean ratio; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Primary immunogenicity subset = a random sample of 175 participants in each vaccine group selected from the full expanded set.

Note: Participants who had no serological or virological evidence (prior to the 1-month post–first study vaccination blood sample collection) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at the first study vaccination and the 1-month post–first study vaccination visits, negative NAAT [nasal swab] at the first study vaccination visit, and any unscheduled visit prior to the 1-month post–first study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.

a. Protocol-specified timing for blood sample collection.
b. n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
d. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titers (monovalent Omicron BA.1 [30 mcg] - Comirnaty [30 mcg]) and the corresponding CI (based on the Student t distribution).

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Table 37: Substudy D – Difference in Percentages of Participants With Seroresponse - Cohort 2 – Primary Immunogenicity Subset - Participants Without Evidence of Infection Up to 1 Month After Dose 4 - Evaluable Immunogenicity Population[149]

		Vaccine Group (as randomized)				
		Monovalent Omicron BA.1 (30 mcg)		TRADENAME (30 mcg)		Difference
Assay	Dose/Sampling Time Point[a]	N[a]	n[b] (%) (95% CI[c])	N[a]	n[b] (%) (95% CI[c])	%[d] (95% CI[e])
SARS-CoV-2 neutralization assay - Omicron BA.1 - NT50 (titre)	1/1 month	130	81 (62.3) (53.4, 70.7)	140	55 (39.3) (31.1, 47.9)	23.0 (11.1, 34.3)

Abbreviations: LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Seroresponse is defined as achieving a ≥ 4-fold rise from baseline (before the first dose of study vaccination). If the baseline measurement is below the LLOQ, the postvaccination measure of ≥4 × LLOQ is considered seroresponse.
Note: Primary immunogenicity subset = a random sample of 175 participants in each vaccine group selected from the full expanded set.
Note: Participants who had no serological or virological evidence (prior to the 1-month post–first study vaccination blood sample collection) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at the first study vaccination and the 1-month post–first study vaccination visits, negative NAAT [nasal swab] at the first study vaccination visit, and any unscheduled visit prior to the 1-month post–first study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.
a. N = number of participants with valid and determinate assay results for the specified assay at both the pre-vaccination time point and the given sampling time point. This value is the denominator for the percentage calculations.
b. n = Number of participants with seroresponse for the given assay at the given sampling time point.
c. Exact 2-sided CI based on the Clopper and Pearson method.
d. Difference in proportions, expressed as a percentage (monovalent Omicron BA.1 [30 mcg] - Comirnaty [30 mcg]).
e. 2-sided CI based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.

5.2. Pharmacokinetic properties

Not applicable.

5.3. Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients[2,3,74,116]

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

TRADENAME (Dilute Before Use)
(4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)
2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC0159)

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1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
Cholesterol
Potassium chloride
Potassium dihydrogen phosphate
Sodium chloride
Disodium hydrogen phosphate dihydrate
Sucrose
Water for injections

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

TRADENAME (Do Not Dilute)

Or

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

TRADENAME (for age 5 years to <12 years)

Or

*[Editorial Guidance for countries: Select this text for the **Tris/Sucrose presentation, 3 micrograms/dose.**]*

TRADENAME (for age 6 months to <5 years)

Or

*[Editorial guidance for countries: Select this text for the **Bivalent (Original/Omicron) presentation, 15/15 micrograms/dose**.]*

TRADENAME (Bivalent)

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

6.2. Incompatibilities

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

6.3. Shelf life

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

TRADENAME (Dilute Before Use)

Unopened vial

12 months at -90 °C to -60 °C.[63,70,83]

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 ºC to -60 ºC; not exceeding the printed expiry date (EXP).[39]

Once removed from the freezer, the unopened vial can be stored for up to 1 month at 2 °C to 8 °C; not exceeding the printed expiry date (EXP). Within the 1-month shelf life at 2 °C to 8 °C, up to 48 hours may be used for transportation.[29,63,117] 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

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

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

TRADENAME (Do Not Dilute)[75]

Or

*[Editorial guidance for countries: Select this text for the **Bivalent (Original/Omicron) presentation, 15/15 micrograms/dose**.]*

TRADENAME (Bivalent)

Unopened vial

12 months when stored at -90 °C to -60 °C.[79,83]

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

Once removed from frozen storage, the unopened vial may be stored refrigerated at 2 °C to 8 °C for a single period of up to 10 weeks; not exceeding the printed expiry date (EXP).[79]

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

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

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

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

Thawed vials can be handled in room light conditions.

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

Opened vial

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Chemical and physical in-use stability has been demonstrated for 12 hours at 2 ºC to 30 ºC. From a microbiological point of view, unless the method of opening precludes the risks of microbial contamination, the product should be used immediately after the first puncture. If not used immediately, in-use storage times and conditions are the responsibility of the user.[77]

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

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

Unopened vial

12 months when stored at -90 °C to -60 °C.[79,83]

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

Once removed from frozen storage, the unopened vial may be stored refrigerated at 2 °C to 8 °C for a single period of up to 10 weeks; not exceeding the printed expiry date (EXP).[79]

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

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

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

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

Thawed vials can be handled in room light conditions.

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

Diluted medicinal product

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

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*[Editorial Guidance for countries: Select this text for the **Tris/Sucrose presentation, 3 micrograms/dose**.]*

TRADENAME (for age 6 months to <5 years)[118]

Unopened vial

12 months when stored at -90 °C to -60 °C.

TRADENAME (for age 6 months to <5 years) will be received frozen at -90 °C to -60 °C.[76] Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

Once removed from frozen storage, the unopened vial may be stored refrigerated at 2 °C to 8 °C for a single period of up to 10 weeks; not exceeding the printed expiry date (EXP).

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

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

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

Vaccine may be stored at temperatures between 8 ºC to 30 ºC for up to 24 hours, including any time at these temperatures following dilution.

Thawed vials can be handled in room light conditions.

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

Diluted medicinal product[119]

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

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6.4. Special precautions for storage[2,25,75,101]

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

TRADENAME (Dilute Before Use)

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

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

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

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

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

TRADENAME (Do Not Dilute)

Or

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

TRADENAME (for age 5 years to <12 years)

Or

*[Editorial Guidance for countries: Select this text for the **Tris/Sucrose presentation, 3 micrograms/dose.]***

TRADENAME (for age 6 months to <5 years)

Or

*[Editorial guidance for countries: Select this text for the **Bivalent (Original/Omicron) presentation, 15/15 micrograms/dose**.]*

TRADENAME (Bivalent)

TRADENAME (Do Not Dilute),TRADENAME (for age 5 years to <12 years), TRADENAME (for age 6 months to <5 years), and {{TRADENAME (Bivalent)}} can be stored in a refrigerator at 2 °C to 8 °C for a single period of up to 10 weeks, not exceeding the original expiry date

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(EXP). Alternatively, the vaccine may be stored in a freezer at -90 °C to -60 °C. The expiry date for storage at -90 °C to -60 °C is printed on the vial and outer carton after "EXP".

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

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

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

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

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

Once thawed, the vaccine cannot be re-frozen.

Thawed vials can be handled in room light conditions.

6.5. Nature and contents of container

Information to be provided by local subsidiary.

6.6. Special precautions for disposal and other handling[2,3,26,29,30,35,63,75,77,78,116,117,118,119,152,153]

Handling instructions

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

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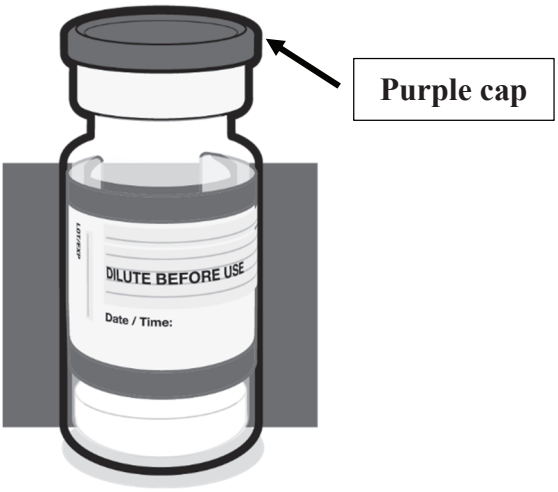
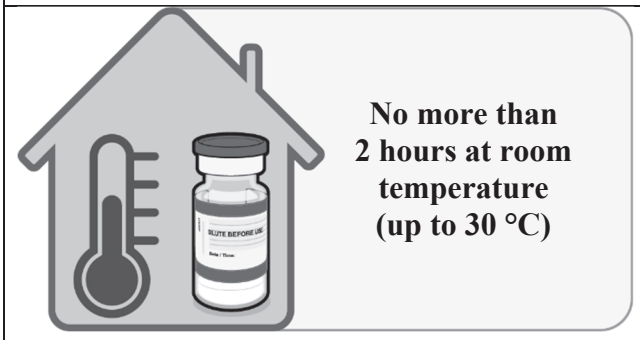
*[Editorial guidance for countries: Select this text for the **PBS/Sucrose presentation, 30 micrograms/dose**.]*

TRADENAME (Dilute Before Use)	
VIAL VERIFICATION	
	Verify that the vial has a purple plastic cap. If the vial has a grey plastic cap, refer to the handling instructions for TRADENAME (Do Not Dilute). If the vial has an orange plastic cap, refer to the handling instructions for TRADENAME (for ages 5 years to <12 years). If the vial has a maroon plastic cap, refer to the handling instructions for TRADENAME (for age 6 months to <5 years).
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; not exceeding the printed expiry date (EXP). Within the 1-month shelf life at 2 °C to 8 °C, up to 48 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.

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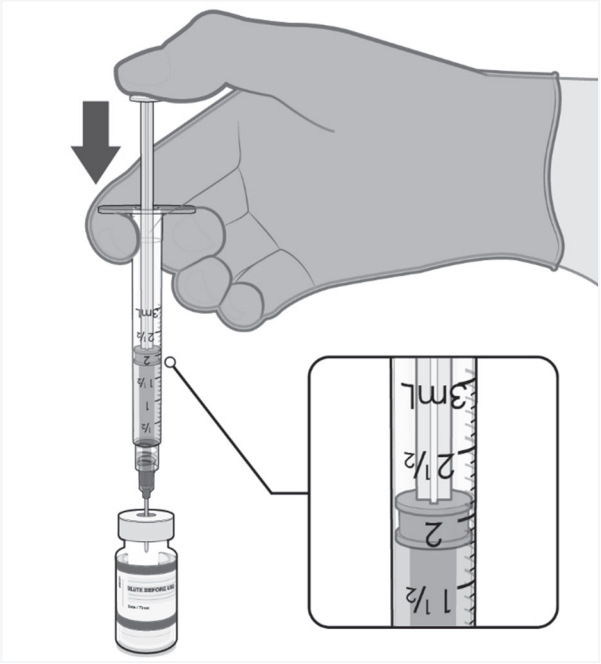
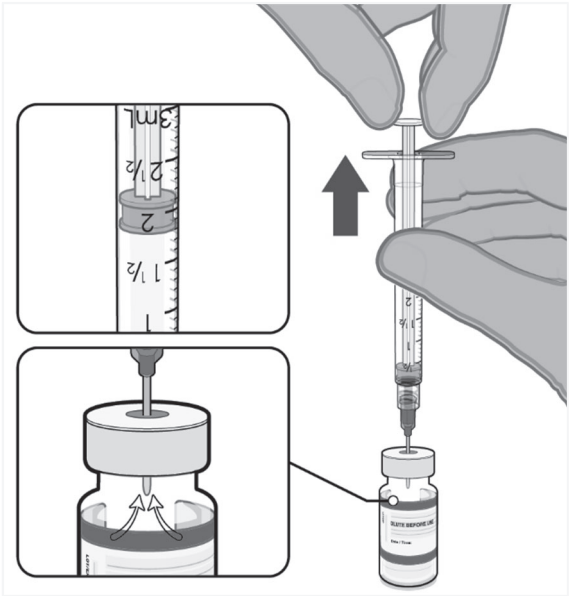
TRADENAME (Dilute Before Use)	
DILUTION	
 **1.8 mL of 0.9% sodium chloride injection**	• The thawed vaccine must be diluted in its original vial with 1.8 mL sodium chloride 9 mg/mL (0.9%) solution for injection, using a 21 gauge or narrower needle and aseptic techniques.
 **Pull back plunger to 1.8 mL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

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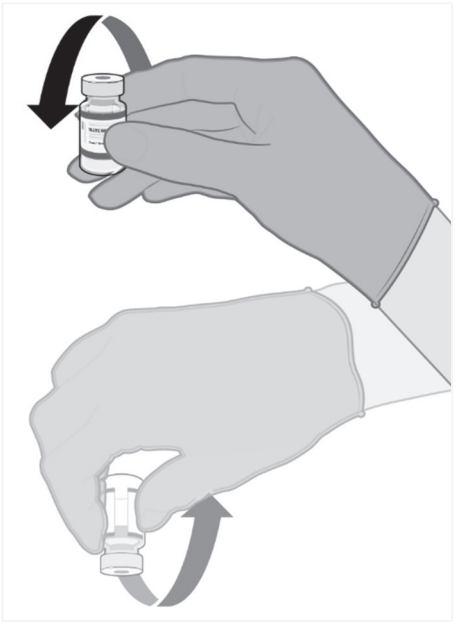
TRADENAME (Dilute Before Use)	
 **Gently × 10**	• Gently invert the diluted dispersion 10 times. Do not shake. • The diluted vaccine should present as an off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discoloration are present.
 **Record appropriate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

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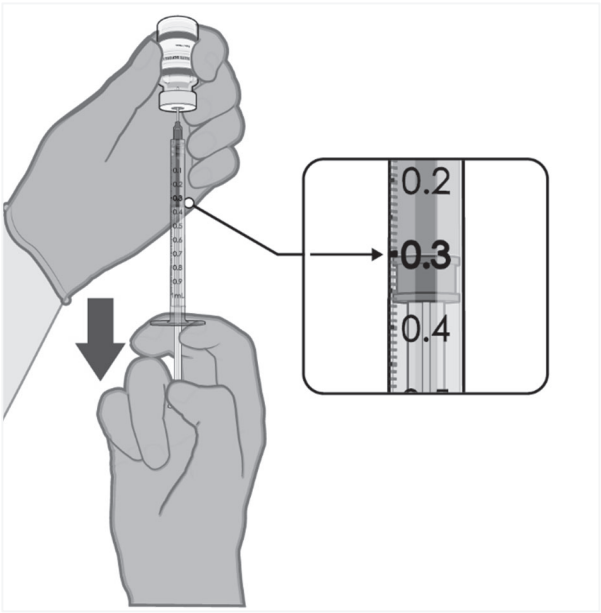
TRADENAME (Dilute Before Use)	
PREPARATION OF INDIVIDUAL 0.3 mL DOSES OF TRADENAME	
 **0.3 mL diluted vaccine**	• After dilution, the vial contains 2.25 mL from which 6 doses of 0.3 mL can be extracted. • Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab. • Withdraw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

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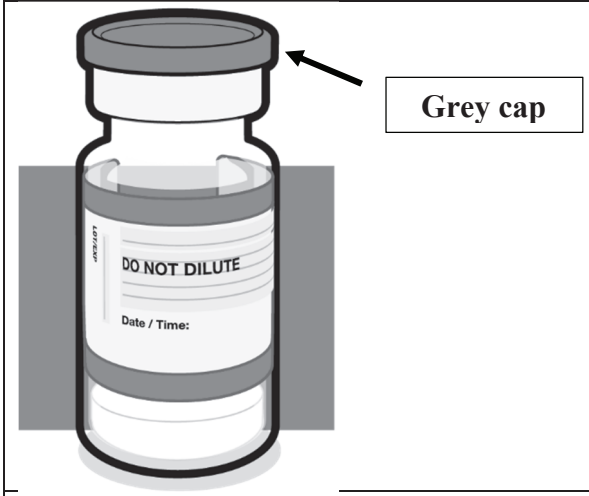
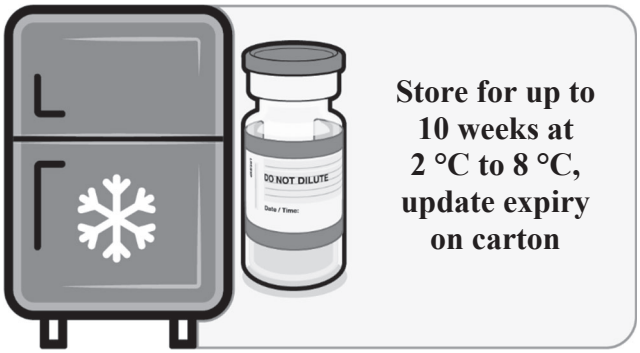
*[Editorial guidance for countries: Select this text for the **Tris/Sucrose presentation, 30 micrograms/dose**.]*

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

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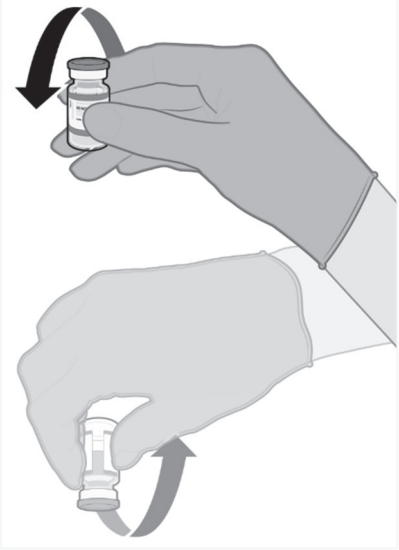
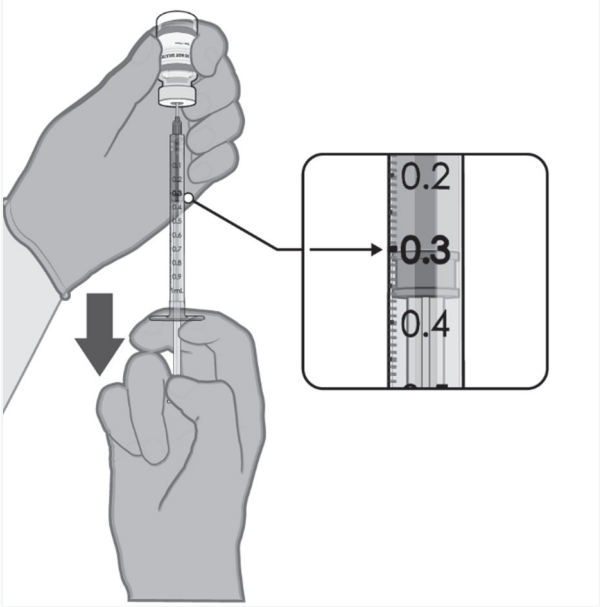
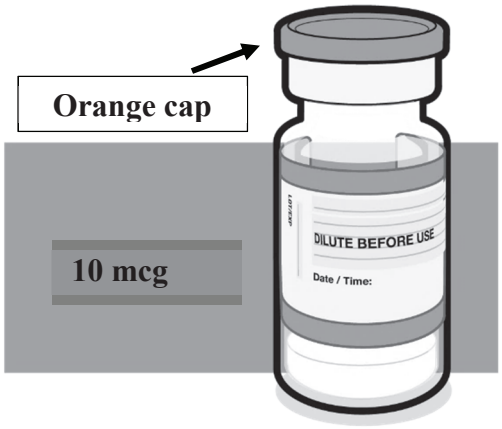
TRADENAME (Do Not Dilute)	
 **Gently × 10**	• Gently mix by inverting vials 10 times prior to use. Do not shake. • Prior to mixing, the thawed dispersion may contain white to off-white opaque amorphous particles. • After mixing, the vaccine should present as a white to off-white dispersion with no particulates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

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

TRADENAME (for age 5 years to <12 years)	
VIAL VERIFICATION	
	• Verify that the vial has an orange plastic cap. If the vial has a purple plastic cap, refer to the handling instructions for TRADENAME (Dilute Before Use). If the vial has a grey plastic cap, refer to the handling instructions for TRADENAME (Do Not Dilute). If the vial has a maroon plastic cap, refer to the handling instructions for TRADENAME (for age 6 months to <5 years).
HANDLING PRIOR TO USE	
	• If the multidose vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 10 vial pack may take 4 hours to thaw. Ensure vials are completely thawed prior to use. • Unopened vials can be stored for up to 10 weeks at 2 °C to 8 °C; not exceeding the printed expiry date (EXP). • Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C for immediate use.

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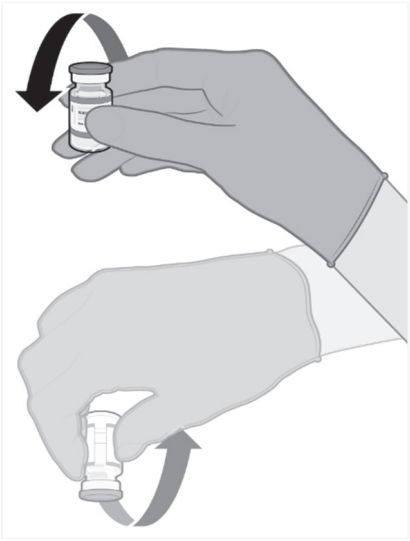
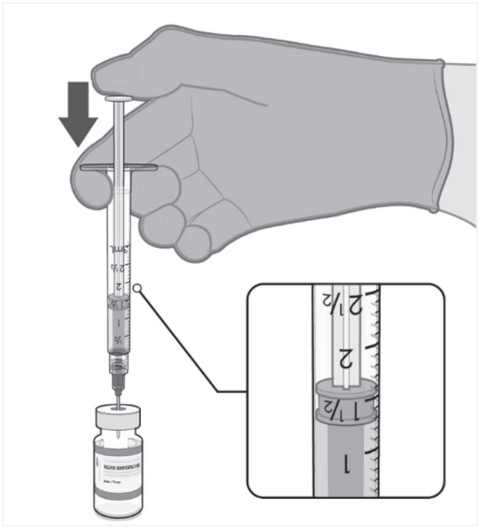
TRADENAME (for age 5 years to <12 years)	
MIXING PRIOR TO DILUTION	
 **Gently × 10**	• Allow the thawed vial to come to room temperature and gently invert it 10 times prior to dilution. Do not shake. • Prior to dilution, the thawed dispersion may contain white to off-white opaque amorphous particles.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

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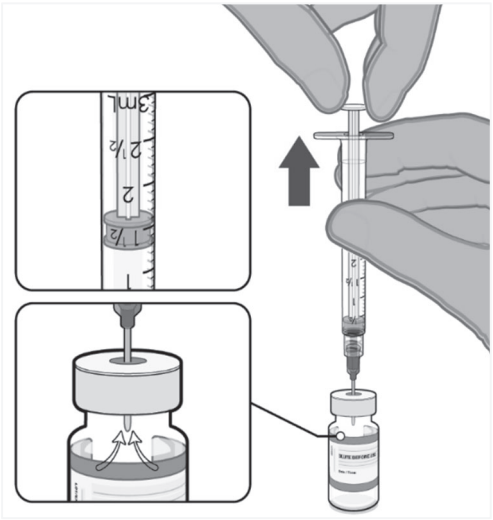
TRADENAME (for age 5 years to <12 years)	
 **Pull back plunger to 1.3 mL to remove air from vial.**	• Equalize vial pressure before removing the needle from the vial stopper by withdrawing 1.3 mL air into the empty diluent syringe.
 **Gently × 10**	• Gently invert the diluted dispersion 10 times. Do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

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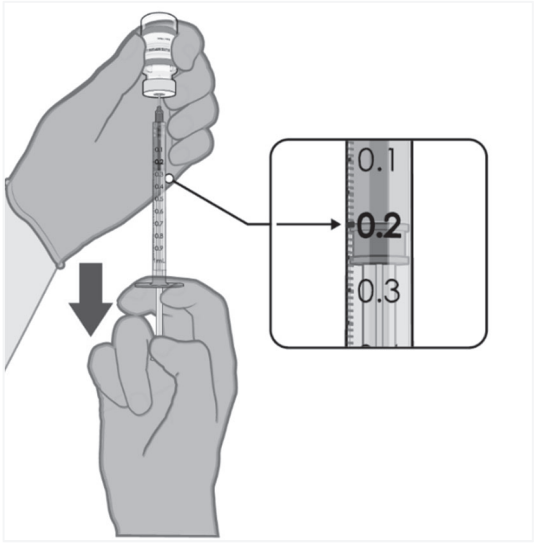
TRADENAME (for age 5 years to <12 years)	
 **Record appropriate date and time.** **Use within 12 hours after dilution.**	• The diluted vials should be marked with the appropriate date and time. • After dilution, store at 2 ºC to 30 ºC and use within 12 hours. • Do not freeze or shake the diluted dispersion.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

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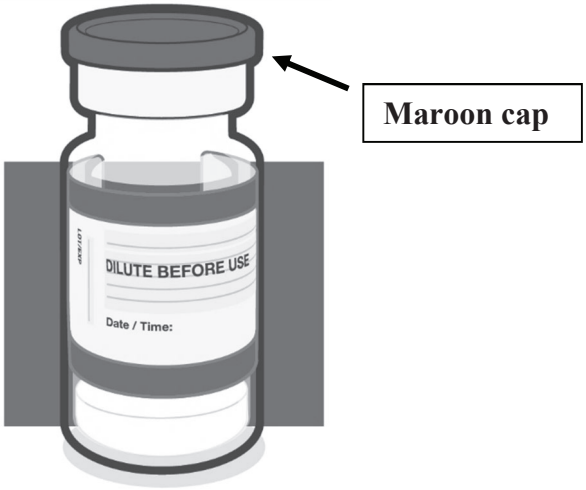
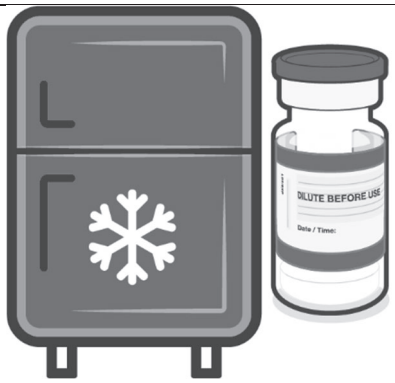
*[Editorial guidance for countries: Select this text for the **Tris/Sucrose presentation, 3 micrograms/dose**.]*

<table>
<tr><th colspan="2">TRADENAME (for age 6 months to <5 years)</th></tr>
<tr><td colspan="2">VIAL VERIFICATION</td></tr>
<tr><td> 

3 mcg</td><td>• Verify that the vial has a maroon plastic cap. If the vial has a purple plastic cap, refer to the handling instructions for TRADENAME (Dilute Before Use). If the vial has a grey plastic cap, refer to the handling instructions for TRADENAME (Do Not Dilute). If the vial has an orange plastic cap, refer to the handling instructions for TRADENAME (for age 5 years to <12 years of age).</td></tr>
<tr><td colspan="2">HANDLING PRIOR TO USE</td></tr>
<tr><td> 

Store for up to 10 weeks at 2 °C to 8 °C</td><td>• If the multidose vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 10 vial pack may take 2 hours to thaw. Ensure vials are completely thawed prior to use.
• Unopened vials can be stored for up to 10 weeks at 2 °C to 8 °C; not exceeding the printed expiry date (EXP).
• Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C for immediate use.</td></tr>
</table>

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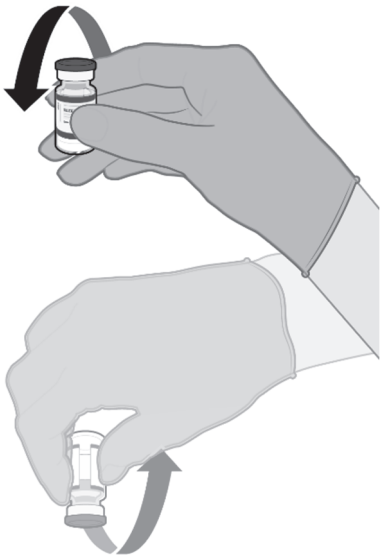
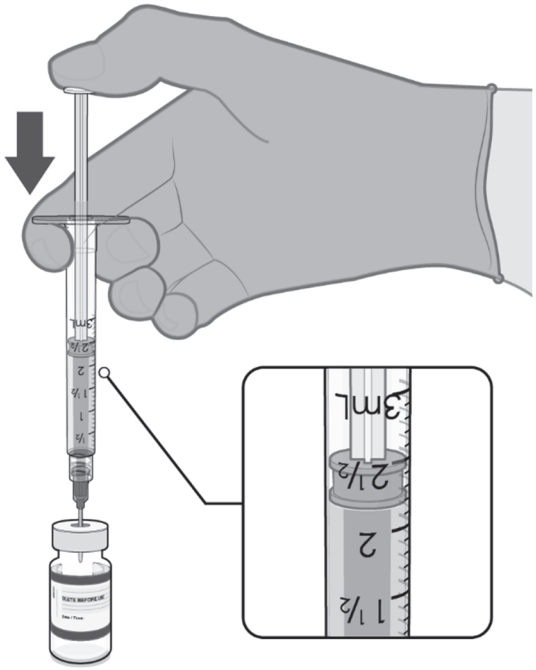
TRADENAME (for age 6 months to <5 years)	
MIXING PRIOR TO DILUTION	
 **Gently × 10**	• Allow the thawed vial to come to room temperature and gently invert it 10 times prior to dilution. Do not shake. • Prior to dilution, the thawed dispersion may contain white to off-white opaque amorphous particles.
DILUTION	
 **2.2 mL of 0.9% sodium chloride**	• The thawed vaccine must be diluted in its original vial with 2.2 mL sodium chloride 9 mg/mL (0.9%) solution for injection, using a 21 gauge or narrower needle and aseptic techniques.

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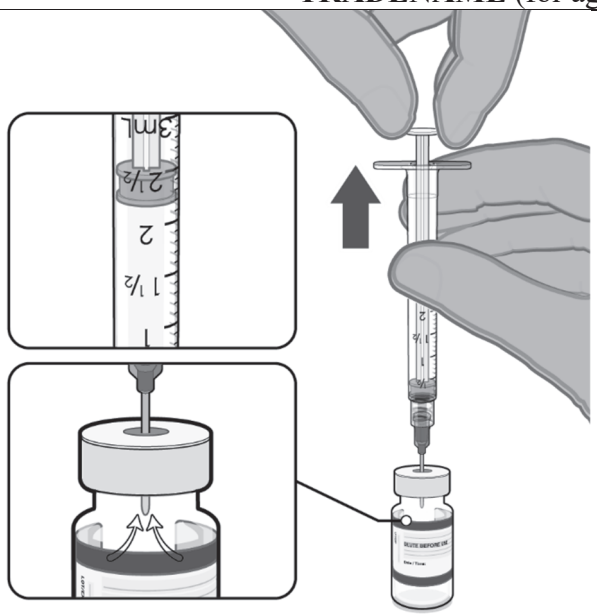
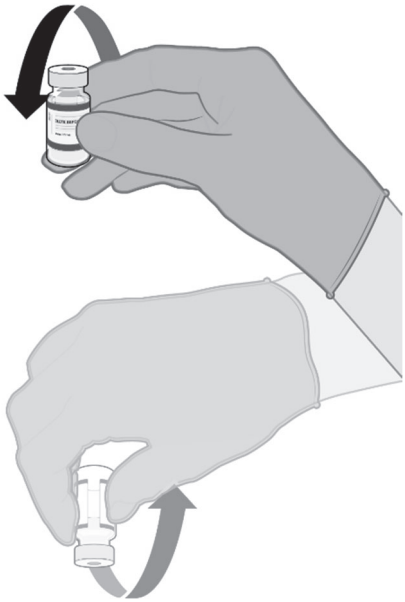
TRADENAME (for age 6 months to <5 years)	
 **Pull back plunger to 2.2 mL to remove air from vial.**	• Equalize vial pressure before removing the needle from the vial stopper by withdrawing 2.2 mL air into the empty diluent syringe.
 **Gently × 10**	• Gently invert the diluted dispersion 10 times. Do not shake. • The diluted vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discoloration are present.

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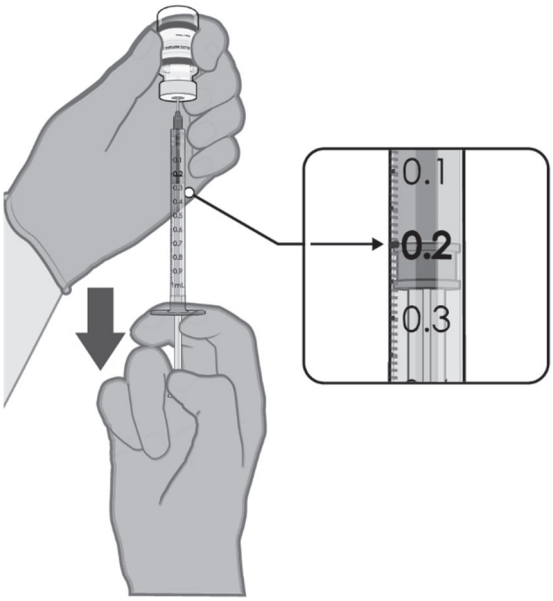
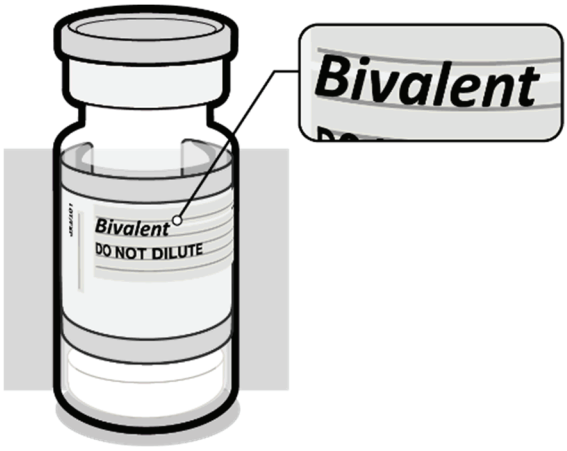
TRADENAME (for age 6 months to <5 years)	
 **Record appropriate date and time.** **Use within 12 hours after dilution.**	• The diluted vials should be marked with the appropriate date and time. • After dilution, store at 2 ºC to 30 ºC and use within 12 hours. • Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.
PREPARATION OF INDIVIDUAL 0.2 mL DOSES OF TRADENAME	
 **0.2 mL diluted vaccine**	• Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab. • Withdraw 0.2 mL of TRADENAME for individuals 6 months through <5 years of age. Low dead-volume syringes and/or needles should be used in order to extract 10 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microliters. If standard syringes and needles are used, there may not be sufficient volume to extract ten doses from a single vial. • Each dose must contain 0.2 mL of vaccine. • If the amount of vaccine remaining in the vial cannot provide a full dose of 0.2 mL, discard the vial and any excess volume. • Discard any unused vaccine within 12 hours after dilution.

*[Editorial guidance for countries: Select this text for the **Bivalent (Original/Omicron) presentation, 15/15 micrograms/dose**]*

TRADENAME (Bivalent)	
VIAL VERIFICATION	
 ✓ **Gray cap and label with gray border.**	• Verify that the vial has a grey cap and a grey border around the label and the product name is TRADENAME (Bivalent) 15/15 micrograms per dose dispersion for injection. • If the vial has a grey plastic cap and a grey border and the product name is TRADENAME 30 micrograms/dose dispersion for injection, please refer to the handling instructions for TRADENAME (Do Not Dilute). • If the plastic cap and border around the label have another color, such as purple, orange, or maroon, please refer to the handling instructions of these TRADENAME vaccines.
HANDLING PRIOR	
 **Store in the refrigerator for up to 10 weeks prior to use.**	• If the multidose vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 10 vial pack may take 6 hours to thaw. Ensure vials are completely thawed prior to use. • Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton. • Unopened vials can be stored for up to 10 weeks at 2 °C to 8 °C; not exceeding the printed expiry date (EXP). • Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C. • Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

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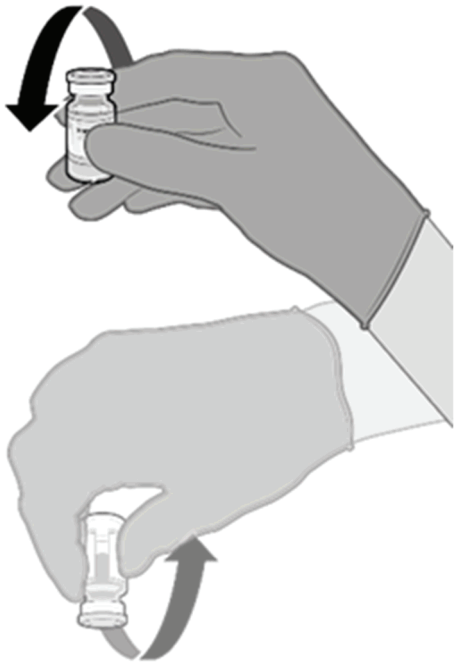 **Gently × 10**	• Gently mix by inverting vials 10 times prior to use. Do not shake. • Prior to mixing, the thawed dispersion may contain white to off-white opaque amorphous particles. • After mixing, the vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the vaccine if particulates or discolouration are present.

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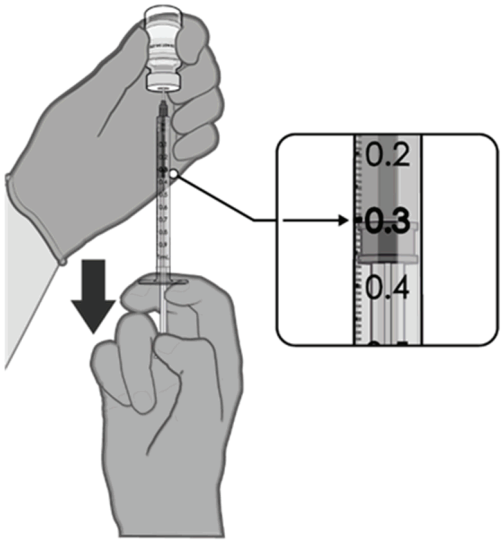
PREPARATION OF INDIVIDUAL 0.3 mL DOSES OF TRADENAME (Bivalent)	
 **Withdraw 0.3 mL dose of vaccine.**	• Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab. • Withdraw 0.3 mL of TRADENAME (Bivalent). Low dead-volume syringes and/or needles should be used in order to extract 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. • Record the appropriate date/time on the vial. Discard any unused vaccine 12 hours after first puncture.

Disposal

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

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7. REFERENCES

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

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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

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41. Module 2.7.4 Summary of Clinical Safety, MAA Type II Variation (12-15 Years) Table 6: Demographic Characteristics – Subjects 12 Through 15 and 16 Through 25 Years of Age – Safety Population
42. Table: Follow-up Time After Dose 2 – Subjects 12 Through 15 Years of Age – Safety Population
43. Table: Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population
44. Table: Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population
45. Table: Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 Through 1 Month After Dose 2, by System Organ Class and Preferred Term – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population
46. Table: Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-up Period – Subjects 12 Through 15 Years of Age and Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
47. Table: Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-up Period – Subjects 12 Through 15 Years of Age and With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
48. Table: Summary of Geometric Mean Ratio – NT50 – Comparison of Subjects 12 Through 15 Years of Age to Subjects 16 Through 25 Years of Age (Immunogenicity Subset) – Subjects Without Evidence of Infection up to 1 Month After Dose 2 – Dose 2 Evaluable Immunogenicity Population
49. Module 2.7.4 Summary of Clinical Safety, COVID-19 Vaccine – MAA Type II Variation (12-15 Years) April 2021
50. Interim Report – 6 Month Update: A Phase 1/2/3, Placebo-Controlled, Randomized, Observer-Blind, Dose-Finding Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of SARS-COV-2 RNA Vaccine Candidates Against COVID-19 in Healthy Individuals [hereafter Interim Report – 6 Month Update] (13 March 2021), Supplemental Table 14.198 Demographic Characteristics, by Age Groups – Phase 2/3 Subjects ≥16 Years of Age – Safety Population
51. Interim Report – 6 Month Update (13 March 2021), Supplemental table 14.84 – Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2 – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 HIV Positive Subjects ≥16 Years of Age – Safety Population
52. Final Analysis Interim Report: A Phase 1/2/3, Placebo-Controlled, Randomized, Observer-Blind, Dose-Finding Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of SARS-COV-2 RNA Vaccine Candidates Against COVID-19 in Healthy

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Individuals (04 November 2020), Section 10.3.3 Phase 2/3, Table 8 Vaccine Administration Timing – ~38000 Subjects for Phase 2/3 Analysis – All Randomized Subjects

53. Interim Report – 6 Month Update (13 March 2021), Table 19. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Subgroup – Blinded Placebo-Controlled Follow-up Period – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
54. Interim Report – 6 Month Update (13 March 2021), Supplemental Table 14.59. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Subgroup– Blinded Placebo-Controlled Follow-up Period–Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
55. Interim Report – 6 Month Update (13 March 2021), Table 20. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – Blinded Placebo-Controlled Follow-up Period – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
56. Interim Report – 6 Month Update (13 March 2021), Table 21. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – Blinded Placebo-Controlled Follow-up Period – Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
57. Interim Report – 6 Month Update (13 March 2021), Table 25. Vaccine Efficacy – First Severe COVID-19 Occurrence From 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-up Period – Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
58. Interim Report – 6 Month Update (13 March 2021), Table 26. Vaccine Efficacy – First Severe COVID-19 Occurrence After Dose 1 – Blinded Placebo-Controlled Follow-up Period – Dose 1 All-Available Efficacy Population
59. Interim Report – 6 Month Update (13 March 2021), Supplemental Table 14.61. Vaccine Efficacy – First Severe COVID-19 Occurrence Based on CDC-Definition After Dose 1 – Blinded Placebo-Controlled Follow-up Period – Dose 1 All-Available Efficacy Population
60. Interim Report – 6 Month Update (13 March 2021), Table 28. Vaccine Efficacy – First Severe COVID-19 Occurrence Based on CDC-Definition From 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-up Period – Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
61. EUA Amendment for Pfizer-BioNTech COVID-19 Vaccine, 6-Month Follow-Up Data from Participants 16 Years of Age and Older (13 March 2021), Section 6.2.1.2.1.2 Efficacy
62. Interim Report – 6 Month Update (13 March 2021), Table 4. Analysis Populations
63. Module 3.2.P.8.1 Stability Summary and Conclusion, August 2021
64. Adverse Drug Reaction Frequency Justification Document, COVID-19 Vaccine (BNT162B2), August 2022
65. Interim Report – 6 Month Update (13 March 2021), Supplemental Table 14.72 – Local Reactions, by Maximum Severity, Within 7 Days After Each Dose (Reactogenicity Subset)

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

66. Interim Report – 6 Month Update (13 March 2021), Supplemental Table 14.79 – Systemic Events, by Maximum Severity, Within 7 Days After Each Dose (Reactogenicity Subset) – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 HIV-Positive Subjects ≥16 Years of Age – Safety Population
67. 2.5 Clinical Overview to Support Inclusion of Vaccine Stress-Related Reactions in Section 4.4 of the Core Data Sheet, May 2021
68. EUA Amendment for Pfizer-BioNTech COVID-19 Vaccine, 6-Month Follow-Up Data from Participants 16 Years of Age and Older (13 March 2021), Section 6.2.2.1.1 Study Populations – BNT162-01 Phase 1 Participants
69. 2.5 Clinical Overview to Support Inclusion of Myocarditis & Pericarditis in Section 4.4 (Special Warnings and Precautions for use) of the Core Data Sheet, July 2021
70. Module 3.2.P.8.3 Stability Data, August 2021
71. Interim Report – BNT162b2 Booster (Dose 3): A Phase 1/2/3, Placebo Controlled, Randomized, Observer-Blind, Dose-Finding Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of SARS-CoV-2 RNA Vaccine Candidates Against COVID-19 in Healthy Individuals
72. Module 3.2.P.2.2 Drug Product – Tris-Sucrose, September 2021
73. Interim Report – Children 5 to <12 Years of Age: A Phase 1, Open-Label Dose-Finding Study to Evaluate Safety, Tolerability, and Immunogenicity and Phase 2/3 Placebo-Controlled, Observer-Blinded Safety, Tolerability, and Immunogenicity Study of a SARS-CoV-2 RNA Vaccine Candidate against COVID-19 in Healthy Children and Young Adults
74. Module 3.2.P.1 Description and Composition of the Drug Product – Tris-Sucrose, September 2021
75. Module 3.2.P.8.1 Stability Summary and Conclusion – Tris-Sucrose, September 2021
76. Module 3.2.P.3.5 Shipping Validation – Tris-Sucrose, September 2021
77. Module 3.2.P.2.6 Compatibility – Tris-Sucrose, September 2021
78. Module 3.2.P.2.3 Manufacturing Process Development – Process Development and Characterization – Tris/Sucrose, September 2021
79. Module 3.2.P.8.1 Stability Summary and Conclusions – Tris-Sucrose, November 2021
80. 2.5 Clinical Overview for Adult Booster Efficacy MAA – Study C4591031, November 2021
81. Interim Clinical Study Report, Protocol C4591001 – Interim Report – Adolescent 6-Month Update: A Phase 1/2/3, Placebo-Controlled, Randomized, Observer-Blind, Dose-Finding Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of SARS-CoV-2 mRNA Vaccine Candidates Against COVID-19 in Healthy Individuals
82. Clinical Information Amendment – COVID-19 Vaccine C4591007 (5 to <12 Years) Efficacy Data in Phase 2/3 Study C4591007, October 2021

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83. Module 3.2.P.8.3 Stability Data, August 2021
84. 2.5 Clinical Overview – Pediatric (5-12 Years) Booster MAA Extension – April 2022
85. Module 3.2.P.2.2 Drug Product – Tris-Sucrose, May 2022
86. 2.5 Clinical Overview – Pediatric (6m-5y) Three-Dose Series MAA Extension - June 2022
87. 2.5 Clinical Overview – BNT162b2 30 mcg Adult Booster (Dose 3) sBLA_MAA – May 2022 - 2.5.1.2.4 Proposed Indication
88. 2.5 Clinical Overview – Pediatric (6m-5y) Three-Dose Series MAA Extension - June 2022 - 2.5.1.2.3.2.2 Phase 1/2/3 Study C4591007
89. 2.5 Clinical Overview – To Support Inclusion of Myocarditis and Pericarditis as Adverse Drug Reactions in Section 4.8 of the Core Data Sheet – July 2022
90. 2.5 Clinical Overview – Pediatric (6m-5y) Three-Dose Series MAA Extension - June 2022 – Table 41. Disposition of All Randomized Participants Prior to Unblinding – Phase 2/3 – 2 to <5 Years of Age, Table 40. Follow-Up Time After Dose 2 or Dose 3 – Phase 2/3 – 2 to <5 Years of Age – Safety Population
91. Module 5 Table: Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Phase 2/3 – Blinded Placebo-Controlled Follow-Up Period – 2 to <5 Years of Age – Safety Population
92. Module 5 Table: Systemic Events, by Maximum Severity, Within 7 days After Each Dose – Phase 2/3 – Blinded Placebo-Controlled Follow-Up Period – 2 to <5 Years of Age – Safety Population
93. 2.5 Clinical Overview – Pediatric (6m-5y) Three-Dose Series MAA Extension - June 2022 - Table 50. Disposition of All Randomized Participants Prior to Unblinding – Phase 2/3 – 6 Months to <2 Years of Age
94. Module 5 Table: Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Phase 2/3 – Blinded Placebo-Controlled Follow-Up Period – 6 Months to <2 Years of Age – Safety Population
95. Module 5 Table: Systemic Events, by Maximum Severity, Within 7 days After Each Dose – Phase 2/3 – Blinded Placebo-Controlled Follow-Up Period – 6 Months to <2 Years of Age – Safety Population
96. Interim Clinical Study Report – C4591001 – 19 May 2022 - Table 12. Follow-up Time After Booster Dose – Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 μg)
97. 2.5 Clinical Overview – BNT162b2 30 mcg Adult Booster (Dose 3)_sBLA_MAA – May 2022 - 2.5.4.4.2.1.2 Duration of Follow-Up – C4591031 – 6 Months Post-Dose 3
98. Interim Full Clinical Study Report – C4591031 Substudy A - 6 Month Analysis – 07 June 2022 – Table 10. Follow-Up Time After Booster Vaccination – Safety Population
99. 2.5 Clinical Overview – Pediatric (6m-5y) Three-Dose Series MAA Extension - June 2022 - Table 28. Demographic Characteristics – Phase 2/3 – 2 to <5 Years of Age – Dose 3 All-Available Efficacy Population

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100. 2.5 Clinical Overview – Pediatric (6m-5y) Three-Dose Series MAA Extension - June 2022 - Table 29. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 3 – Blinded Follow-Up Period – Phase 2/3 – 2 to <5 Years of Age – Dose 3 All-Available Efficacy Population
101. 2.5 Clinical Overview – Pediatric (6m-5y) Three-Dose Series MAA Extension - June 2022 – Table 7. Demographic Characteristics – Immunobridging Subset – Participants Without Evidence of Infection – Study C4591007 Phase 2/3 2 to <5 Years of Age and Study C4591001 Phase 2/3 16 Through 25 Years of Age – Evaluable Immunogenicity Population
102. 2.5 Clinical Overview – Pediatric (6m-5y) Three-Dose Series MAA Extension - June 2022 - Table 8. Summary of Geometric Mean Ratios – NT50 – Participants Without Evidence of Infection – Immunobridging Subset – Study C4591007 Phase 2/3 2 to <5 Years of Age (1 Month After Dose 3) and Study C4591001 Phase 2/3 16 Through 25 Years of Age (1 Month After Dose 2) – Evaluable Immunogenicity Population
103. 2.5 Clinical Overview – Pediatric (6m-5y) Three-Dose Series MAA Extension - June 2022 - Table 9. Difference in Percentages of Participants With Seroresponse – Participants Without Evidence of Infection – Immunobridging Subset – Comparison of Study C4591007 Phase 2/3 2 to <5 Years of Age (1 Month After Dose 3) and Study C4591001 Phase 2/3 16 Through 25 Years of Age (1 Month After Dose 2) – Evaluable Immunogenicity Population
104. 2.5 Clinical Overview – Pediatric (6m-5y) Three-Dose Series MAA Extension - June 2022 - Table 34. Demographic Characteristics – Phase 2/3 – 6 Months to <2 Years of Age – Dose 3 All-Available Efficacy Population
105. 2.5 Clinical Overview – Pediatric (6m-5y) Three-Dose Series MAA Extension - June 2022 - Table 35. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 3 – Blinded Follow-Up Period – Phase 2/3 – 6 Months to <2 Years of Age – Dose 3 All-Available Efficacy Population
106. 2.5 Clinical Overview – Pediatric (6m-5y) Three-Dose Series MAA Extension - June 2022 – Table 17. Demographic Characteristics – Immunobridging Subset – Participants Without Evidence of Infection – Study C4591007 Phase 2/3 6 Months to <2 Years of Age and Study C4591001 Phase 2/3 16 Through 25 Years of Age – Evaluable Immunogenicity Population
107. 2.5 Clinical Overview – Pediatric (6m-5y) Three-Dose Series MAA Extension - June 2022 – Table 18. Summary of Geometric Mean Ratios – NT50 – Participants Without Evidence of Infection – Immunobridging Subset – Study C4591007 Phase 2/3 6 Months to <2 Years of Age (1 Month After Dose 3) and Study C4591001 Phase 2/3 16 Through 25 Years of Age (1 Month After Dose 2) – Evaluable Immunogenicity Population
108. 2.5 Clinical Overview – Pediatric (6m-5y) Three-Dose Series MAA Extension - June 2022 – Table 19. Difference in Percentages of Participants With Seroresponse – Participants Without Evidence of Infection – Immunobridging Subset – Comparison of Study C4591007 Phase 2/3 6 Months to <2 Years of Age (1 Month After Dose 3) and Study C4591001 Phase 2/3 16 Through 25 Years of Age (1 Month After Dose 2) – Evaluable Immunogenicity Population
109. Module 5.3.5.1. Table: Geometric Mean Ratio – Comparison of 1 Month After Booster Dose to 1 Month After Dose 2 – Phase 3 – BNT162b2 – Experienced Subjects Without

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Evidence of Infection up to 1 Month After Booster Dose Who Were Rerandomized to Receive 1 Booster Dose (30 ug) – Dose 3 Booster Evaluable Immunogenicity Population

110. Interim Clinical Study Report – C4591001 – 19 May 2022 – Table 4 Analysis Populations
111. Module 5.3.5.1. Table: Percentage Difference of Subjects Achieving Seroresponse – Comparison of 1 Month After Booster Dose to 1 Month After Dose 2 – Phase 3 – BNT162b2 – Experienced Subjects Without Evidence of Infection up to 1 Month After Booster Dose Who Were Rerandomized to Receive 1 Booster Dose (30 ug) – Dose 3 Booster Evaluable Immunogenicity Population
112. 2.5 Clinical Overview – BNT162b2 30 mcg Adult Booster (Dose 3) sBLA_MAA – May 2022 – 2.5.4.4.2.5 Efficacy Conclusions – C4591031 – 6 Months Post-Dose 3
113. 2.5 Clinical Overview – BNT162b2 30 mcg Adult Booster (Dose 3) sBLA_MAA – May 2022 – 2.5.4.4.2.1.2 Duration of Follow-Up - C4591031 - 6 Month Post-Dose 3, Table 14. Follow-Up Time After Booster Vaccination – Participants Without Evidence of Infection Prior to 7 Days After Booster Vaccination – Evaluable Efficacy Population
114. 2.5 Clinical Overview – BNT162b2 30 mcg Adult Booster (Dose 3) sBLA_MAA – May 2022 – 2.5.4.4.2.2 Confirmed COVID-19 Cases – C4591031 – 6 Months Post-Dose 3, Table 16. Vaccine Efficacy - First COVID-19 Occurrence From 7 Days After Booster Vaccination – Blinded Follow-Up Period – Participants Without Evidence of Infection Prior to 7 Days After Booster Vaccination – Evaluable Efficacy Population
115. 2.5 Clinical Overview – BNT162b2 30 mcg Adult Booster (Dose 3) sBLA_MAA – May 2022 – 2.5.4.4.2.2 Confirmed COVID-19 Cases – C4591031 – 6 Months Post-Dose 3, Table 17. Vaccine Efficacy - First COVID-19 Occurrence From 7 Days After Booster Vaccination – Blinded Follow-Up Period – Participants With or Without Evidence of Infection Prior to 7 Days After Booster Vaccination – Evaluable Efficacy Population
116. Module 3.2.P.1 Description and Composition of the Drug Product – Tris-Sucrose – May 2022
117. Module 3.2.P.3.5 Process Validation and/or Evaluation – Shipping Validation – June 2022
118. Module 3.2.P.8.1 Stability Summary and Conclusion – Tris-Sucrose – May 2022
119. Module 3.2.P.2.6 Compatibility – Tris-Sucrose – May 2022
120. Module 3.2.S.1.1 Nomenclature, Omicron BA.4/BA.5 – July 2022
121. 2.5 Clinical Overview – BNT162b2– Omicron Modified Vaccine (C4591031 SSE)_MAA_July 2022 – 2.5.6.3 Benefit-Risk Conclusions
122. Interim Full Clinical Study Report – Protocol C4591031 Substudy D: Substudy D Interim Report – Cohort 2 – 1-Month Analysis: A Phase 3 Master Protocol to Evaluate Additional Dose(s) of BNT162b2 in Healthy Individuals Previously Vaccinated With BNT162b2 – Section 3.1 Overview of Study Design - 10 June 2022
123. Interim Full Clinical Study Report – Protocol C4591031 Substudy D: Substudy D Interim Report – Cohort 2 – 1-Month Analysis: A Phase 3 Master Protocol to Evaluate Additional Dose(s) of BNT162b2 in Healthy Individuals Previously Vaccinated With BNT162b2 – Section 4.1 Disposition of Participants – Cohort 2 - 10 June 2022

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124. Interim Full Clinical Study Report – Protocol C4591031 Substudy D – Section 4.7 Duration of Follow-UP - 10 June 2022
125. Interim Full Clinical Study Report – Protocol C4591031 Substudy D: Substudy D Interim Report – Cohort 2 – 1-Month Analysis: A Phase 3 Master Protocol to Evaluate Additional Dose(s) of BNT162b2 in Healthy Individuals Previously Vaccinated With BNT162b2 – Section 5.2.1. Local Reactions - 10 June 2022
126. Interim Full Clinical Study Report – Protocol C4591031 Substudy D: Substudy D Interim Report – Cohort 2 – 1-Month Analysis: A Phase 3 Master Protocol to Evaluate Additional Dose(s) of BNT162b2 in Healthy Individuals Previously Vaccinated With BNT162b2 – Section 5.2.2. Systemic Events - 10 June 2022
127. Interim Full Clinical Study Report – Protocol C4591031 Substudy E – Table 7. Demographic Characteristics – Expanded Cohort – Participants >55 Years of Age – Safety Population - 16 July 2022
128. Interim Full Clinical Study Report – Protocol C4591031 Substudy E – Table 5. Follow-up Time After Study Vaccination – Expanded Cohort – Participants >55 Years of Age – Safety Population - 16 July 2022
129. Interim Full Clinical Study Report – Protocol C4591031 Substudy E – Section 5.1.2.3.1.2 Adverse Events from Study Vaccination to Data Cutoff Date - 16 July 2022
130. Interim Full Clinical Study Report – Protocol C4591031 Substudy E – Table 21. Number (%) of Participants Reporting at Least 1 Adverse Event From the Study Vaccination Through 1 Month After the Study Vaccination, by System Organ Class and Preferred Term — Expanded Cohort — Participants >55 Years of Age — Safety Population – 16 July 2022
131. Interim Full Clinical Study Report – Protocol C4591031 Substudy E – Supplemental Table 14.38 Systemic Events, by Maximum Severity, Within 7 Days After the Study Vaccination – Expanded Cohort – Participants >55 Years of Age – Safety Population - 16 July 2022
132. Interim Full Clinical Study Report – Protocol C4591031 Substudy E – Supplemental Table 14.26 Local Reactions, by Maximum Severity, Within 7 Days After the Study Vaccination – Expanded Cohort – Participants >55 Years of Age – Safety Population - 16 July 2022
133. 2.5 Clinical Overview – BNT162b2– Omicron Modified Vaccine (C4591031 SSE)_MAA_July 2022 – Section 2.5.1.2.3.2.1. Study C4591031 Substudy E
134. 2.5 Clinical Overview – BNT162b2– Omicron Modified Vaccine (C4591031 SSE)_MAA_July 2022 – Section 2.5.5.2.1.1. Safety Population Characteristics – C4591031 Substudy E (Expanded Cohort)
135. Module 5.3.5.1 – Table – Demographic Characteristics – Expanded Cohort – Participants >55 Years of Age – Safety Population
136. 2.5 Clinical Overview – BNT162b2– Omicron Modified Vaccine (C4591031 SSE)_MAA_July 2022 – 2.5.5.2.1.3.1. Overview of Adverse Events
137. 2.5 Clinical Overview – BNT162b2– Omicron Modified Vaccine (C4591031 SSE)_MAA_July 2022 – 2.5.5.2.1.3.1.1. Adverse Events by System Organ Class and Preferred Term, Adverse Events from Study Vaccination to Data Cutoff Date

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138. 2.5 Clinical Overview – BNT162b2– Omicron Modified Vaccine (C4591031 SSE)_MAA_July 2022 – 2.5.5.2.1.2. Reactogenicity – C4591031 Substudy E (Expanded Cohort)
139. 2.5 Clinical Overview – BNT162b2– Omicron Modified Vaccine (C4591031 SSE)_MAA_July 2022 – 2.5.5.2.1.8. Safety Conclusions – C4591031 Substudy E
140. Interim Full Clinical Study Report – Protocol C4591031 Substudy E – Table 7. Demographic Characteristics – Expanded Cohort – Participants >55 Years of Age – Safety Population - 16 July 2022
141. 2.5 Clinical Overview – BNT162b2– Omicron Modified Vaccine (C4591031 SSE)_MAA_July 2022 – 2.5.1.1.1.1. Immunogenicity Endpoints and Analysis Methods – C4591031 Substudy E, Immunogenicity Analysis Methods - C4591031 Substudy E
142. 2.5 Clinical Overview – BNT162b2– Omicron Modified Vaccine (C4591031 SSE)_MAA_July 2022 – 2.5.4.2.1.2.1.1. GMR of Omicron BA.1 Neutralizing Titres
143. 2.5 Clinical Overview – BNT162b2– Omicron Modified Vaccine (C4591031 SSE)_MAA_July 2022 – Table 4. Difference in Percentages of Participants With Seroresponse – Participants Without Evidence of Infection up to 1 Month After the Study Vaccination – Expanded Cohort – Immunogenicity Subset – Participants >55 Years of Age – Evaluable Immunogenicity Population
144. 2.5 Clinical Overview – BNT162b2– Omicron Modified Vaccine (C4591031 SSE)_MAA_July 2022 – Table 2. Geometric Mean Ratios For Between Vaccine Group Comparison – Participants Without Evidence of Infection up to 1 Month After the Study Vaccination – Expanded Cohort – Immunogenicity Subset – Participants >55 Years of Age – Evaluable Immunogenicity Population
145. 2.5 Clinical Overview – BNT162b2– Omicron Modified Vaccine (C4591031 SSE)_MAA_July 2022 – Table 4. Difference in Percentages of Participants With Seroresponse – Participants Without Evidence of Infection up to 1 Month After the Study Vaccination – Expanded Cohort – Immunogenicity Subset – Participants >55 Years of Age – Evaluable Immunogenicity Population
146. Interim Full Clinical Study Report – Protocol C4591031 Substudy D: Substudy D Interim Report – Cohort 2 – 1-Month Analysis: A Phase 3 Master Protocol to Evaluate Additional Dose(s) of BNT162b2 in Healthy Individuals Previously Vaccinated With BNT162b2 – Table 4. Disposition of All Randomized Participants - Cohort 2 - 10 June 2022
147. Interim Full Clinical Study Report – Protocol C4591031 Substudy D: Substudy D Interim Report – Cohort 2 – 1-Month Analysis: A Phase 3 Master Protocol to Evaluate Additional Dose(s) of BNT162b2 in Healthy Individuals Previously Vaccinated With BNT162b2 – Section 3.1. Overview of Study Design - 10 June 2022
148. Interim Full Clinical Study Report – Protocol C4591031 Substudy D: Substudy D Interim Report – Cohort 2 – 1-Month Analysis: A Phase 3 Master Protocol to Evaluate Additional Dose(s) of BNT162b2 in Healthy Individuals Previously Vaccinated With BNT162b2 – Section 5.1.1.1. Superiority Analysis - GMR of Omicron-Neutralizing Titers in BNT162b2 OMI Dose 4 Recipients Compared to BNT162b2 Dose 4 Recipients - 10 June 2022

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149. Interim Full Clinical Study Report – Protocol C4591031 Substudy D: Substudy D Interim Report – Cohort 2 – 1-Month Analysis: A Phase 3 Master Protocol to Evaluate Additional Dose(s) of BNT162b2 in Healthy Individuals Previously Vaccinated With BNT162b2 – Table 11 - 10 June 2022

150. Interim Full Clinical Study Report – Protocol C4591031 Substudy D: Substudy D Interim Report – Cohort 2 – 1-Month Analysis: A Phase 3 Master Protocol to Evaluate Additional Dose(s) of BNT162b2 in Healthy Individuals Previously Vaccinated With BNT162b2 – Section 5.4.1. Immunogenicity, Descriptive Immunogenicity Analyses – Full Expanded Set - 10 June 2022

151. Interim Full Clinical Study Report – Protocol C4591031 Substudy D: Substudy D Interim Report – Cohort 2 – 1-Month Analysis: A Phase 3 Master Protocol to Evaluate Additional Dose(s) of BNT162b2 in Healthy Individuals Previously Vaccinated With BNT162b2 – Table 10 - 10 June 2022

152. Module 3.2.P.1 Description and composition of the drug product – July 2022

153. Module 3.2.P.2.3 Process development and characterization – July 2022

154. 2.5 Clinical Overview – BNT162b2– Omicron Modified Vaccine (C4591031 SSE)_MAA_July 2022 – 2.5.4.2.1.2.1.2. Seroresponse Rate to Omicron BA.1 Strain

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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)

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)[64]

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

a. Source: Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2, by System Organ Class and Preferred Term – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 Subjects ≥16 Years of Age – Safety Population (Study C4591001, Cut-off 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 (Study C4591001, Cut-off 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 (Study C4591001, Cut-off date: 13March2021).
d. These adverse reactions were identified in the post-authorization period.
e. Due to the cross-over design of clinical trials, the actual incidence of myocarditis and pericarditis cannot be reliably estimated however, based on published literature presented in the Clinical Overview, the CIOMS frequency category for myocarditis and pericarditis is "very rare."[89]

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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)[64]

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]	
Cardiac disorders	Myocarditis[d]	N/A[f]
	Pericarditis[d]	N/A[f]
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 (Study C4591001, Cut-off 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 (Study C4591001, Cut-off 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 (Study C4591001, Cut-off date: 13March2021).
d. These adverse reactions were identified in the post-authorization period.
e. The following reactions were not reported in the 12 through 15 year old age group in Study C4591001: angioedema, pruritus, malaise, lethargy, asthenia, decreased appetite, hyperhidrosis, and night sweats but are still considered adverse reactions for this age group.
f. Due to the cross-over design of clinical trials, the actual incidence of myocarditis and pericarditis cannot be reliably estimated however, based on published literature presented in the Clinical Overview, the CIOMS frequency category for myocarditis and pericarditis is "very rare."[89]

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Table A-3. Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency within each System Organ Class: Individuals 5 Through <12 Years of Age (06 September 2021 Data Cut-off Date)[64]

System Organ Class	ADR Term	Frequency n/N (%)
Blood and lymphatic system disorders	Lymphadenopathy	13/1518 (0.9%)[a]
Immune system disorders	Anaphylaxis[d]	Not known
	Hypersensitivity reactions	
	Rash[d]	5/1518 (0.3%)[a]
	Urticaria[d]	3/1518 (0.2%)[a]
	Pruritus[d]	1/1518 (0.1%)[a]
	Angioedema[d,e]	
Metabolism and nutrition disorders	Decreased appetite	1/1518 (0.1%)[a]
Nervous system disorders	Headache	579/1517 (38.2%)[b]
	Lethargy[e]	
Cardiac disorders	Myocarditis[d,e]	N/A[f]
	Pericarditis[d,e]	N/A[f]
Gastrointestinal disorders	Diarrhea[d]	146/1517 (9.6%)[b]
	Vomiting[d]	60/1517 (4.0%)[b]
	Nausea	6/1518 (0.4%)[a]
Skin and subcutaneous tissue disorders	Hyperhidrosis[e]	
	Night sweats[e]	
Musculoskeletal and connective tissue disorders	Myalgia (muscle pain)	266/1517 (17.5%)[b]
	Arthralgia (joint pain) (new)	115/1517 (7.6%)[b]
	Pain in extremity (arm)[d]	3/1518 (0.2%)[a]
General disorders and administration site conditions	Injection site pain	1279/1517 (84.3%)[c]
	Fatigue	785/1517 (51.7%)[b]
	Injection site redness	401/1517 (26.4%)[c]
	Injection site swelling	309/1517 (20.4%)[c]
	Chills	188/1517 (12.4%)[b]
	Pyrexia	126/1517 (8.3%)[b]
	Malaise	2/1518 (0.1%)[a]
	Asthenia[e]	

a. Source: Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2, by System Organ Class and Preferred Term – Phase 2/3 – 5 to <12 Years of Age – Safety Population (Study C4591007, Cut-off date: 06Sep2021).
b. Source: Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Phase 2/3 – 5 to <12 Years of Age – Safety Population (Study C4591007, Cut-off date: 06Sep2021).
c. Source = Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Phase 2/3 – 5 to <12 Years of Age – Safety Population (Study C4591007, Cut-off date: 06Sep2021).
d. These adverse reactions were identified in the post-authorization period.
e. At the time of the data cut-off date, the following reactions were not reported in participants 5 through <12 years of age in Study C4591007: **Error! Reference source not found.**angioedema, lethargy, myocarditis, pericarditis, asthenia, hyperhidrosis, and night sweats but are still considered adverse reactions for this age group.
f. Due to the cross-over design of clinical trials, the actual incidence of myocarditis and pericarditis cannot be reliably estimated however, based on published literature presented in the Clinical Overview, the CIOMS frequency category for myocarditis and pericarditis is "very rare."[89]

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Table A-4. Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency Within Each System Organ Class: Individuals 2 to <5 Years of Age (29 April 2022 Data Cut-off Date)[64]

System Organ Class	ADR Term	Frequency n/N (%)
Blood and lymphatic system disorders	Lymphadenopathy	1/1835 (0.1%)[a]
Immune system disorders	Anaphylaxis[d]	Not known
	Hypersensitivity reactions	
	Rash[d,e]	6/1835 (0.3%)[a]
	Urticaria[d]	6/1835 (0.3%)[a]
	Pruritis[d,f]	
	Angioedema[d,f]	
Metabolism and nutrition disorders	Decreased appetite	1/1835 (0.1%)[a]
Nervous system disorders	Headache	159/1826 (8.7%)[b]
	Lethargy[f]	
Cardiac disorders	Myocarditis[d,f]	N/A[g]
	Pericarditis[d,f]	N/A[g]
Gastrointestinal disorders	Diarrhea[d]	248/1826 (13.6%)[b]
	Vomiting[d]	117/1826 (6.4%)[b]
	Nausea	2/1835 (0.1%)[a]
Skin and subcutaneous tissue disorders	Hyperhidrosis[f]	
	Night sweats[f]	
Musculoskeletal and connective tissue disorders	Myalgia (muscle pain)	92/1826 (5.0%)[b]
	Arthralgia (joint pain) (new)	44/1826 (2.4%)[b]
	Pain in extremity (arm)[d]	3/1835 (0.2%)[a]
General disorders and administration site conditions	Injection site pain	858/1826 (47.0%)[c]
	Fatigue	818/1826 (44.8%)[b]
	Injection site redness	346/1833 (18.9%)[c]
	Pyrexia	192/1832 (10.5%)[b]
	Injection site swelling	154/1833 (8.4%)[c]
	Chills	104/1826 (5.7%)[b]
	Asthenia	1/1835 (0.1%)[a]
	Malaise[f]	

a. Source: Number (%) of Participants Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 3, by System Organ Class and Preferred Term – Phase 2/3 – Blinded Placebo-Controlled Follow-Up Period – 2 to <5 Years of Age – Safety Population (Study C4591007, Cutoff date: 29Apr2022)
b. Source = Systemic Events, by Maximum Severity, Within 7 Days After Each Dose –Phase 2/3 – Blinded Placebo Controlled Follow-Up Period – 2 to <5 Years of Age – Safety Population (Study C4591007, Cutoff date: 06Sep2021)
c. Source = Local Reactions, by Maximum Severity, Within 7 Days After Each Dose –Phase 2/3 – Blinded Placebo-Controlled Follow-Up Period – 2 to <5 Years of Age – Safety Population (Study C4591007, Cutoff date: 29Apr2022)
d. These adverse reactions were identified in the post-authorization period.
e. The frequency of rash was calculated as follows: Rash (n=4), Rash erythematous (n=1), Rash maculo-papular (n=1) (4+1+1=6/1835=0.3%).
f. At the time of the data-lock the following reactions were not reported in participants 2 to <5 Years of Age in Study C4591007: pruritus, angioedema, lethargy, myocarditis, pericarditis, hyperhidrosis, night sweats, and malaise but are still considered adverse reactions for this age group.
g. Due to the cross-over design of clinical trials, the actual incidence of myocarditis and pericarditis cannot be reliably estimated however, based on published literature presented in the Clinical Overview, the CIOMS frequency category for myocarditis and pericarditis is "very rare."[89]

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Table A-5. Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency Within Each System Organ Class: Individuals 6 Months to <2 Years of Age (29 April 2022 Data Cut-off Date)[64]

System Organ Class	ADR Term	Frequency n/N (%)
Blood and lymphatic system disorders	Lymphadenopathy	2/1178 (0.2%)[a]
Immune system disorders	Anaphylaxis[d]	Not known
	Hypersensitivity reactions	
	Rash[d,e]	13/1178 (1.1%)[a]
	Urticaria[d]	8/1178 (0.7%)[a]
	Pruritis[d,f]	
	Angioedema[d,f]	
Metabolism and nutrition disorders	Decreased appetite	451/1169 (38.6%)[b]
Psychiatric disorders	Irritability	800/1169 (68.4%)[b]
Nervous system disorders	Headache	2/1178 (0.2%)[a]
	Lethargy	1/1178 (0.1%)[a]
Cardiac disorders	Myocarditis[d,f]	N/A[g]
	Pericarditis[d,f]	N/A[g]
Gastrointestinal disorders	Vomiting[d]	47/1178 (4.0%)[a]
	Diarrhea[d]	39/1178 (3.3%)[a]
	Nausea[f]	
Skin and subcutaneous tissue disorders	Hyperhidrosis[f]	
	Night sweats[f]	
Musculoskeletal and connective tissue disorders	Myalgia (muscle pain)[f]	
	Arthralgia (joint pain) (new)[f]	
	Pain in extremity (arm)[d,f]	
General disorders and administration site conditions	Injection site tenderness	309/1169 (26.4%)[c]
	Injection site redness	210/1177 (17.8%)[c]
	Pyrexia	169/1177 (14.4%)[b]
	Injection site swelling	86/1177 (7.3%)[c]
	Fatigue	8/1178 (0.7%)[a]
	Chills	1/1178 (0.1%)[a]
	Malaise[f]	
	Asthenia[f]	

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Table A-5. Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency Within Each System Organ Class: Individuals 6 Months to <2 Years of Age (29 April 2022 Data Cut-off Date)[64]

a. Source: Number (%) of Participants Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 3, by System Organ Class and Preferred Term – Phase 2/3 – Blinded Placebo-Controlled Follow-Up Period – 6 months to <2 Years of Age – Safety Population (Study C4591007, Cutoff date: 29Apr2022)
b. Source = Systemic Events, by Maximum Severity, Within 7 Days After Each Dose –Phase 2/3 – Blinded Placebo-Controlled Follow-Up Period – 6 months to <2 Years of Age – Safety Population (Study C4591007, Cutoff date: 29Apr2022)
c. Source = Local Reactions, by Maximum Severity, Within 7 Days After Each Dose –Phase 2/3 – Blinded Placebo-Controlled Follow-Up Period – 6 months to <2 Years of Age – Safety Population (Study C4591007, Cutoff date: 29Apr2022)
d. These adverse reactions were identified in the post-authorization period.
e. The frequency of rash was calculated as follows: Rash (n=8), Rash macular (n=1), Rash maculo-papular (n=2); Rash papular (n=1); Rash erythematous (n=1) (8+1+2+1+1=13/1178=1.1%)
f. At the time of the data cut-off date, the following reactions were not reported in participants 6 months to <2 Years of Age in Study C4591007: pruritus, angioedema, myocarditis, pericarditis, nausea, hyperhidrosis, night sweats, myalgia, arthralgia, pain in extremity, malaise, and asthenia but are still considered adverse reactions for this age group.
g. Due to the cross-over design of clinical trials, the actual incidence of myocarditis and pericarditis cannot be reliably estimated however, based on published literature presented in the Clinical Overview, the CIOMS frequency category for myocarditis and pericarditis is “very rare.”[89]

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Table A-6. Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency Within Each System Organ Class: BNT162b2-Experienced Subjects (18 to 55 Years of Age) Who Were Rerandomized to Receive 1 Booster (Dose 3) of BNT162b2 (30 µg) – Booster Safety Population (17 June 2021 Data Cut-off Date)[*,64]

System Organ Class	ADR Term	Frequency n/N (%)
Blood and lymphatic system disorders	Lymphadenopathy	16/306 (5.2%)[a,b]
Immune system disorders	Anaphylaxis[e]	Not known
	Hypersensitivity reactions	
	Rash[e]	1/306 (0.3%)[b]
	Pruritus[e,f]	
	Urticaria[e,f]	
	Angioedema[e,f]	
Metabolism and nutrition disorders	Decreased appetite	1/306 (0.3%)[b]
Nervous system disorders	Headache	140/289 (48.4%)[c]
	Lethargy[f]	
Cardiac disorders	Myocarditis[e]	N/A[g]
	Pericarditis[e]	N/A[g]
Gastrointestinal disorders	Diarrhea[e]	25/289 (8.7%)[c]
	Vomiting[e]	5/289 (1.7%)[c]
	Nausea	2/306 (0.7%)[b]
Skin and subcutaneous tissue disorders	Hyperhidrosis[f]	
	Night sweats[f]	
Musculoskeletal and connective tissue disorders	Myalgia (muscle pain)	113/289 (39.1%)[c]
	Arthralgia (joint pain) (new)	73/289 (25.3%)[c]
	Pain in extremity (arm)[e]	1/306 (0.3%)[b]
General disorders and administration site conditions	Injection site pain	240/289 (83.0%)[d]
	Fatigue	184/289 (63.7%)[c]
	Chills	84/289 (29.1%)[c]
	Pyrexia	25/289 (8.7%)[c]
	Injection site swelling	23/289 (8.0%)[d]
	Injection site redness	17/289 (5.9%)[d]
	Malaise[f]	
	Asthenia[f]	

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

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

b. Source: Number (%) of Subjects Reporting at Least 1 Adverse Event From Booster Dose to 1 Month After Booster Dose, by System Organ Class and Preferred Term – Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) – Booster Safety Population (Study C4591001, Cut-off date: 17June2021).

c. Source = Systemic Events, by Maximum Severity, Within 7 Days After Booster Dose Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) – Booster Safety Population (Study C4591001, Cut-off date: 17June2021).

d. Source = Local Reactions, by Maximum Severity, Within 7 Days After Booster Dose – Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) –Booster Safety Population (Study C4591001, Cut-off date: 17June2021).

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

f. The following reactions were not reported in the booster safety population in Study C4591001: angioedema, pruritus, urticaria, malaise, lethargy, asthenia, hyperhidrosis, and night sweats but are still considered adverse reactions.

g. Due to the cross-over design of clinical trials, the actual incidence of myocarditis and pericarditis cannot be reliably estimated however, based on published literature presented in the Clinical Overview, the CIOMS frequency category for myocarditis and pericarditis is “very rare.”[89]

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Table A-7. Adverse Drug Reaction Table of Non-reactogenicity Reactions[a] with Preferred Terms Listed by Decreasing Frequency Within Each System Organ Class: BNT162b2-Experienced Subjects (≥16 Years of Age) Who Received 1 Booster (Dose 3) of BNT162b2 (30 µg) in Study C4591031 Substudy A (SSA) – Booster Safety Population (5 October 2021 Data Cut-off Date)[64,80]

System Organ Class	ADR Term	Frequency n/N (%)
Blood and lymphatic system disorders	Lymphadenopathy[b]	141/5055 (2.8%)[c]
Immune system disorders	Anaphylaxis[d]	Not known
	Hypersensitivity reactions	
	Rash[d]	3/5055 (0.1%)[c]
	Pruritus[d]	3/5055 (0.1%)[c]
	Urticaria[d]	2/5055 (0.04%)[c]
	Angioedema[d,e]	
Metabolism and nutrition disorders	Decreased appetite	9/5055 (0.2%)[c]
Nervous system disorders	Headache[a]	
	Lethargy	12/5055 (0.2%)[c]
Cardiac disorders	Myocarditis[d]	N/A[f]
	Pericarditis[d]	N/A[f]
Gastrointestinal disorders	Diarrhea[a,d]	
	Vomiting[a,d]	
	Nausea	48/5055 (0.9%)[c]
Skin and subcutaneous tissue disorders	Night sweats	5/5055 (0.1%)[c]
	Hyperhidrosis	4/5055 (0.1%)[c]
Musculoskeletal and connective tissue disorders	Myalgia (muscle pain)[a]	
	Arthralgia (joint pain) (new)[a]	
	Pain in extremity (arm)[d]	54/5055 (1.1%)[c]
General disorders and administration site conditions	Injection site pain[a]	
	Fatigue[a]	
	Chills[a]	
	Pyrexia[a,g]	
	Injection site swelling[a]	
	Injection site redness[a]	
	Malaise	35/5055 (0.7%)[c]
	Asthenia	8/5055 (0.2%)[c]

a. Please see Table A-6 for the frequency of the following reactogenicity adverse reactions that were reported in the booster safety population of Study C4591001: headache, diarrhea, vomiting, myalgia (muscle pain), arthralgia (joint pain) (new), injection site pain, fatigue, chills, pyrexia, injection site swelling, injection site redness.

b. A higher frequency of lymphadenopathy (2.8% vs. 0.4%) was observed in participants receiving a booster dose (in Study C4591031) compared to participants receiving 2 doses. The frequency of lymphadenopathy was calculated as follows: Lymphadenopathy (n=135), Lymph node pain (n=4), Lymphadenitis (n=2) (135+4+2=141/5055=2.8%).

c. Source: Number (%) of Participants Reporting at Least 1 Adverse Event From Booster Vaccination to 1 Month After Booster Vaccination, by System Organ Class and Preferred Term – Blinded Follow-up Period – Safety Population (Study C4591031 SSA, Cut-off date: 05October2021).

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

e. The following reaction was not reported in the Study C4591031: angioedema but it is still considered an adverse reactions.

f. Due to the cross-over design of clinical trials, the actual incidence of myocarditis and pericarditis cannot be reliably estimated however, based on published literature presented in the Clinical Overview, the CIOMS frequency category for myocarditis and pericarditis is "very rare."[89]

g. The preferred term pyrexia is a cluster term also covering 'body temperature increased'.

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Table A-8. Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency Within Each System Organ Class: Individuals 18 to 55 years old Who Received a Booster (Dose 4) of BNT162b2 30 µg in Study C4591031 Substudy D (SSD) — Safety Population (11 March 2022 Data Cut-off Date)[64]

System Organ Class	ADR Term	Frequency n/N (%)
Blood and lymphatic system disorders	Lymphadenopathy	3/325 (0.9%)[a]
Immune system disorders	Anaphylaxis[b]	
	Hypersensitivity reactions	
	Rash[b,c]	
	Pruritus[b,c]	
	Urticaria[b,c]	
	Angioedema[b,c]	
Metabolism and nutrition disorders	Decreased appetite[c]	
Nervous system disorders	Headache	138/306 (45.1%)[d]
	Lethargy[c]	
Cardiac disorders	Myocarditis[b]	N/A[e]
	Pericarditis[b]	N/A[e]
Gastrointestinal disorders	Diarrhea[b]	36/306 (11.8%)[d]
	Vomiting[b]	5/306 (1.6%)[d]
	Nausea[c]	
Skin and subcutaneous tissue disorders	Hyperhidrosis[c]	
	Night sweats[c]	
Musculoskeletal and connective tissue disorders	Myalgia (muscle pain)	87/306 (28.4%)[d]
	Arthralgia (joint pain) (new)	46/306 (15.0%)[d]
	Pain in extremity (arm)[b,c]	
General disorders and administration site conditions	Injection site pain	240/306 (78.4%)[f]
	Fatigue	185/306 (60.5%)[d]
	Chills	80/306 (26.1%)[d]
	Injection site swelling	27/306 (8.8%)[f]
	Pyrexia	22/306 (7.2%)[d]
	Injection site redness	13/306 (4.2%)[f]
	Malaise[c]	
	Asthenia[c]	

a. Source: Number (%) of Participants Reporting at Least 1 Adverse Event From First Study Vaccination Through 1 Month After First Study Vaccination, by System Organ Class and Preferred Term - Cohort 2 - Safety Population (Study C4591031 SSD, Cutoff date: 11 March 2022)
b. These adverse reactions were identified in the post-authorization period.
c. At the time of the data cut-off date, the following reactions were not reported in the safety population in Study C4591031 SSD: rash, pruritus, urticaria, angioedema, decreased appetite, lethargy, nausea, hyperhidrosis, night sweats, pain in extremity, malaise, and asthenia but are still considered adverse reactions.
d Source = Systemic Events, by Maximum Severity, Within 7 Days After First Study Vaccination - Cohort 2 - Safety Population (Study C4591031 SSD, Cutoff date: 11 March 2022)
e. Due to the cross-over design of clinical trials, the actual incidence of myocarditis and pericarditis cannot be reliably estimated however, based on published literature presented in the Clinical Overview, the CIOMS frequency category for myocarditis and pericarditis is "very rare."[89]
f. Source = Local Reactions, by Maximum Severity, Within 7 Days After First Study Vaccination - Cohort 2 - Safety Population (Study C4591031 SSD, Cutoff date: 11 March 2022)

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Table A-9. Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency Within Each System Organ Class: Individuals >55 years old Who Received a Booster (Dose 4) of BNT162b2 30 µg in Study C4591031 Substudy E (SSE) – Expanded Cohort – Safety Population (16 May 2022 Data Cut-off Date)[64]

System Organ Class	ADR Term	Frequency n/N (%)
Blood and lymphatic system disorders	Lymphadenopathy	1/305 (0.3%)[a]
Immune system disorders	Anaphylaxis[b]	
	Hypersensitivity reactions	
	Rash[b,c]	
	Pruritus[b,c]	
	Urticaria[b,c]	
	Angioedema[b,c]	
Metabolism and nutrition disorders	Decreased appetite[c]	
Nervous system disorders	Headache	79/298 (26.5%)[d]
	Lethargy[c]	
Cardiac disorders	Myocarditis[b]	N/A[e]
	Pericarditis[b]	N/A[e]
Gastrointestinal disorders	Diarrhea[b]	13/298 (4.4%)[d]
	Vomiting[b]	4/298 (1.3%)[d]
	Nausea	1/305 (0.3%)[a]
Skin and subcutaneous tissue disorders	Hyperhidrosis[c]	
	Night sweats[c]	
Musculoskeletal and connective tissue disorders	Myalgia (muscle pain)	59/298 (19.8%)[d]
	Arthralgia (joint pain) (new)	27/298 (9.1%)[d]
	Pain in extremity (arm)[b]	1/305 (0.3%)[a]
General disorders and administration site conditions	Injection site pain	179/298 (60.1%)[f]
	Fatigue	135/298 (45.3%)[d]
	Chills	49/298 (16.4%)[d]
	Injection site redness	19/298 (6.4%)[f]
	Injection site swelling	18/298 (6.0%)[f]
	Pyrexia	11/298 (3.7%)[d]
	Malaise[c]	
	Asthenia[c]	

a. Source: Number (%) of Participants Reporting at Least 1 Adverse Event From the Study Vaccination Through 1 Month After the Study Vaccination, by System Organ Class and Preferred Term — Expanded Cohort — Participants >55 Years of Age — Safety Population (Study C4591031 SSE, Cutoff date: 16 May 2022)
b. These adverse reactions were identified in the post-authorization period.
c. At the time of the data cut-off date, the following reactions were not reported in the safety population in Study C4591031 SSE: rash, pruritus, urticaria, angioedema, decreased appetite, lethargy, hyperhidrosis, night sweats, malaise and asthenia but are still considered ADRs.
d. Source = Systemic Events, by Maximum Severity, Within 7 Days After the Study Vaccination – Expanded Cohort – Participants >55 Years of Age – Safety Population (Study C4591031 SSE, Cutoff date: 16 May 2022)
e. Due to the cross-over design of clinical trials, the actual incidence of myocarditis and pericarditis cannot be reliably estimated however, based on published literature presented in the Clinical Overview, the CIOMS frequency category for myocarditis and pericarditis is "very rare."[89]
f. Source = Local Reactions, by Maximum Severity, Within 7 Days After the Study Vaccination – Expanded Cohort – Participants >55 Years of Age – Safety Population (Study C4591031 SSE, Cutoff date: 16 May 2022)

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Table A-10. Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency Within Each System Organ Class: Individuals 18 to 55 years old Who Received a Booster (Dose 4) of Monovalent BNT162b2 OMI BA.1 (30 ug) in Study C4591031 Substudy D (SSD) – Safety Population (11 March 2022 Data Cut-off Date)[64]

System Organ Class	ADR Term	Frequency n/N (%)
Blood and lymphatic system disorders	Lymphadenopathy[a]	2/315 (0.6%)[b]
Immune system disorders	Anaphylaxis[c]	
	Hypersensitivity reactions	
	Rash[c,d]	
	Pruritus[c,d]	
	Urticaria[c,d]	
	Angioedema[c,d]	
Metabolism and nutrition disorders	Decreased appetite[d]	
Nervous system disorders	Headache	140/294 (47.6%)[e]
	Lethargy[d]	
Cardiac disorders	Myocarditis[c]	N/A[f]
	Pericarditis[c]	N/A[f]
Gastrointestinal disorders	Diarrhea[c]	25/294 (8.5%)[e]
	Vomiting[c]	8/294 (2.7%)[e]
	Nausea[d]	
Skin and subcutaneous tissue disorders	Hyperhidrosis[d]	
	Night sweats	1/315 (0.3%)[b]
Musculoskeletal and connective tissue disorders	Myalgia (muscle pain)	99/294 (33.7%)[e]
	Arthralgia (joint pain) (new)	69/294 (23.5%)[e]
	Pain in extremity (arm)[c,d]	
General disorders and administration site conditions	Injection site pain	229/294 (77.9%)[g]
	Fatigue	189/294 (64.3%)[e]
	Chills	93/294 (31.6%)[e]
	Pyrexia	25/294 (8.5%)[e]
	Injection site swelling	25/294 (8.5%)[g]
	Injection site redness	21/294 (7.1%)[g]
	Malaise[d]	
	Asthenia[d]	

a. The frequency of lymphadenopathy was calculated as follows: Lymphadenopathy (n=1), axillary pain (n=1) (1+1=2/315=0.6%)
b. Source: Number (%) of Participants Reporting at Least 1 Adverse Event From First Study Vaccination Through 1 Month After First Study Vaccination, by System Organ Class and Preferred Term - Cohort 2 - Safety Population (Study C4591031 SSD, Cutoff date: 11 March 2022)
c. These adverse reactions were identified in the post-authorization period.
d. At the time of the data cut-off date, the following reactions were not reported in the safety population in Study C4591031 SSD: rash, pruritus, urticaria, angioedema, decreased appetite, lethargy, nausea, hyperhidrosis, pain in extremity, malaise, and asthenia but are still considered ADRs.
e. Source = Systemic Events, by Maximum Severity, Within 7 Days After First Study Vaccination - Cohort 2 - Safety Population (Study C4591031 SSD, Cutoff date: 11 March 2022)
f. Due to the cross-over design of clinical trials, the actual incidence of myocarditis and pericarditis cannot be reliably estimated however, based on published literature presented in the Clinical Overview, the CIOMS frequency category for myocarditis and pericarditis is "very rare."[89]
g. Source = Local Reactions, by Maximum Severity, Within 7 Days After First Study Vaccination - Cohort 2 – Safety Population (Study C4591031 SSD, Cutoff date: 11 March 2022)

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Table A-11. Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency Within Each System Organ Class: Individuals >55 years old Who Received a Booster (Dose 4) of Bivalent BNT162b2 (15 µg) + BNT162b2 OMI BA.1 (15 µg) in Study C4591031 Substudy E (SSE) – Expanded Cohort – Safety Population (16 May 2022 Data Cut-off Date)[64]

System Organ Class	ADR Term	Frequency n/N (%)
Blood and lymphatic system disorders	Lymphadenopathy	1/305 (0.3%)[a]
Immune system disorders	Anaphylaxis[b]	
	Hypersensitivity reactions	
	Rash[b,c]	
	Pruritus[b,c]	
	Urticaria[b,c]	
	Angioedema[b,c]	
Metabolism and nutrition disorders	Decreased appetite[c]	
Nervous system disorders	Headache	101/301 (33.6%)[d]
	Lethargy[c]	
Cardiac disorders	Myocarditis[b]	N/A[e]
	Pericarditis[b]	N/A[e]
Gastrointestinal disorders	Diarrhea[b]	27/301 (9.0%)[d]
	Vomiting[b]	5/301 (1.7%)[d]
	Nausea	1/305 (0.3%)[a]
Skin and subcutaneous tissue disorders	Hyperhidrosis[c]	
	Night sweats[c]	
Musculoskeletal and connective tissue disorders	Myalgia (muscle pain)	67/301 (22.3%)[d]
	Arthralgia (joint pain) (new)	34/301 (11.3%)[d]
	Pain in extremity (arm)[b,c]	
General disorders and administration site conditions	Injection site pain	175/301 (58.1%)[f]
	Fatigue	148/301 (49.2%)[d]
	Chills	39/301 (13.0%)[d]
	Injection site redness	21/301 (7.0%)[f]
	Injection site swelling	20/301 (6.6%)[f]
	Pyrexia	15/301 (5.0%)[d]
	Malaise	1/305 (0.3%)[a]
	Asthenia[c]	

a. Source: Number (%) of Participants Reporting at Least 1 Adverse Event From the Study Vaccination Through 1 Month After the Study Vaccination, by System Organ Class and Preferred Term — Expanded Cohort — Participants >55 Years of Age — Safety Population (Study C4591031 SSE, Cutoff date: 16May2022)
b. These adverse reactions were identified in the post-authorization period.
c. At the time of the data cut-off date, the following reactions were not reported in the safety population in Study C4591031 SSE: rash, pruritus, urticaria, angioedema, decreased appetite, lethargy, hyperhidrosis, night sweats, pain in extremity and asthenia but are still considered adverse reactions.
d. Source = Systemic Events, by Maximum Severity, Within 7 Days After the Study Vaccination – Expanded Cohort – Participants >55 Years of Age – Safety Population (Study C4591031 SSE, Cutoff date: 16May2022)
e. Due to the cross-over design of clinical trials, the actual incidence of myocarditis and pericarditis cannot be reliably estimated however, based on published literature presented in the Clinical Overview, the CIOMS frequency category for myocarditis and pericarditis is "very rare."[89]
f. Source = Local Reactions, by Maximum Severity, Within 7 Days After the Study Vaccination – Expanded Cohort – Participants >55 Years of Age – Safety Population (Study C4591031 SSE, Cutoff date: 16May2022)

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Table A-12. Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency Within Each System Organ Class: Individuals 5 Through <12 Years of Age Who Received a Booster Dose (Dose 3) of BNT162b2 (22 March 2022 Data Cut-off Date)[*,64,84]

System Organ Class	ADR Term	Frequency n/N (%)
Blood and lymphatic system disorders	Lymphadenopathy[a]	10/401 (2.5%)[b]
Immune system disorders	Anaphylaxis[e]	Not known
	Hypersensitivity reactions	
	Rash[e]	1/401 (0.2%)[b]
	Urticaria[e,f]	
	Pruritus[e,f]	
	Angioedema[e,f]	
Metabolism and nutrition disorders	Decreased appetite[f]	
Nervous system disorders	Headache	126/371 (34.0%)[c]
	Lethargy[f]	
Cardiac Disorders	Myocarditis[e,f]	N/A[g]
	Pericarditis[e,f]	N/A[g]
Gastrointestinal disorders	Diarrhea[e]	18/371 (4.9%)[c]
	Vomiting[e]	9/371 (2.4%)[c]
	Nausea[f]	
Skin and subcutaneous tissue disorders	Hyperhidrosis[f]	
	Night sweats[f]	
Musculoskeletal and connective tissue disorders	Myalgia (muscle pain)	68/371 (18.3%)[c]
	Arthralgia (joint pain) (new)	25/371 (6.7%)[c]
	Pain in extremity (arm)[e,f]	
General disorders and administration site conditions	Injection site pain	274/371 (73.9%)[d]
	Fatigue	169/371 (45.6%)[c]
	Injection site swelling	61/371 (16.4%)[d]
	Injection site redness	58/371 (15.6%)[d]
	Chills	39/371 (10.5%)[c]
	Pyrexia	25/371 (6.7%)[c]
	Malaise[f]	
	Asthenia[f]	

* Booster dose (Dose 3) of BNT162b2 10 µg was administered to participants 5 through <12 years of age in Study C4591007.

a. A higher frequency of lymphadenopathy was observed in participants 5 through <12 years of age in Study C4591007 (2.5% vs. 0.9%) receiving a booster dose compared to participants receiving 2 doses. The frequency of lymphadenopathy was calculated as follows: lymphadenopathy (n = 8), lymph node palpable (n = 1), axillary mass (n = 1) (8+1+1 = 10/401 = 2.5%).

b. Source: Number (%) of Participants Reporting at Least 1 Adverse Event From Dose 3 to 1 Month After Dose 3, by System Organ Class and Preferred Term – Phase 2/3 – Participants Who Received Dose 3 of BNT162b2 – 5 to <12 Years of Age – Safety Population (Study C4591007, Cut-off date: 22 March 2022).

c. Source = Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Phase 2/3 – Participants Who Received Dose 3 of BNT162b2 – 5 to <12 Years of Age – Safety Population (Study C4591007, Cut-off date: 22 March 2022).

d. Source = Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Phase 2/3 – Participants Who Received Dose 3 of BNT162b2 – 5 to <12 Years of Age – Safety Population (Study C4591007, Cut-off date: 22 March 2022).

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

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f. At the time of the data cut-off date, the following reactions were not reported in participants 5 through <12 Years of Age in Study C4591007 after Dose 3: urticaria, pruritus, angioedema, decreased appetite, lethargy, myocarditis, pericarditis, nausea, night sweats, hyperhidrosis, pain in extremity (arm), malaise, asthenia but are still considered adverse reactions.

g. Due to the cross-over design of clinical trials, the actual incidence of myocarditis and pericarditis cannot be reliably estimated however, based on published literature presented in the Clinical Overview, the CIOMS frequency category for myocarditis and pericarditis is "very rare."[89]

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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

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)[64]

System Organ Class	Very Common ≥1/10 (≥10%)	Common ≥1/100 to <1/10 (≥1% to <10%)	Uncommon ≥1/1,000 to <1/100 (≥0.1% to <1%)	Rare ≥1/10,000 to <1/1,000 (≥0.01% to <0.1%)	Very Rare <1/10,000 (<0.01%)	Frequency not known (cannot be estimated from the available data)
Blood and lymphatic system disorders			Lymphadenopathy			
Immune system disorders			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			
Cardiac disorders					Myocarditis[a]; Pericarditis[a]	
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			

* CIOMS frequency categories are based on clinical trial C4591001 crude incidence and was reported to only one significant figure.

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.

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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)[64]

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

* CIOMS frequency categories are based on clinical trial C4591001 crude incidence and was reported to only one significant figure.

a. These adverse reactions were identified in the post-authorization period. The following events were not reported in the 12 through 15 years of age group in Study C4591001: angioedema, pruritus, malaise, lethargy, asthenia, decreased appetite, hyperhidrosis, and night sweats but are still considered adverse reactions for this age group.

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

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Table B-3. ADRs by System Organ Class and CIOMS Frequency Category* Listed in Order of Decreasing Medical Seriousness Within Each Frequency Category and System Organ Class: Individuals 5 Through <12 Years of Age (06 September 2021 Data Cut-off Date)[64]

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

* CIOMS frequency categories are based on clinical trial C4591007 crude incidence and was reported to only one significant figure.

a. These adverse reactions were identified in the post-authorization period. At the time of the data cut-off date, the following reactions were not reported in participants 5 through <12 years of age in Study C4591007: angioedema, lethargy, myocarditis, pericarditis, asthenia, hyperhidrosis, and night sweats but are still considered adverse reactions for this age group.

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

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Table B-4. ADRs by System Organ Class and CIOMS Frequency Category* Listed in order of Decreasing Medical Seriousness Within Each Frequency Category and System Organ Class: Individuals 2 to <5 Years of Age (29 April 2022 Data Cut-off Date)[64]

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

* CIOMS frequency categories are based on clinical trial C4591007 crude incidence and was reported to only one significant figure.

a. These adverse reactions were identified in the post-authorization period. At the time of the data cut-off date, the following reactions were not reported in participants 2 to <5 Years of Age in Study C4591007: pruritus, angioedema, lethargy, myocarditis, pericarditis, hyperhidrosis, night sweats, and malaise but are still considered adverse reactions for this age group.

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

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Table B-5. ADRs by System Organ Class and CIOMS Frequency Category* Listed in Order of Decreasing Medical Seriousness Within Each Frequency Category and System Organ Class: Individuals 6 Months to <2 Years of Age (29 April 2022 Data Cut-off Date)[64]

System Organ Class	Very Common ≥1/10 (≥10%)	Common ≥1/100 to <1/10 (≥1% to <10%)	Uncommon ≥1/1,000 to <1/100 (≥0.1% to <1%)	Rare ≥1/10,000 to <1/1,000 (≥0.01% to <0.1%)	Very Rare <1/10,000 (<0.01%)	Frequency not known (cannot be estimated from the available data)
Blood and lymphatic system disorders			Lymphadenopathy			
Immune system disorders		Rash[a,b]	Urticaria[a,b]			Anaphylaxis[a]
Metabolism and nutrition disorders	Decreased appetite					
Psychiatric disorders	Irritability					
Nervous system disorders			Headache Lethargy			
Gastrointestinal disorders		Vomiting[a,] Diarrhea[a]				
General disorders and administration site conditions	Injection site tenderness; Injection site redness; Pyrexia	Injection site swelling	Fatigue; Chills			

* CIOMS frequency categories are based on clinical trial C4591007 crude incidence and was reported to only one significant figure.

a. These adverse reactions were identified in the post-authorization period. At the time of the data cut-off date, the following reactions were not reported in participants 6 months to <2 Years of Age in Study C4591007: pruritus, angioedema, myocarditis, pericarditis, nausea, hyperhidrosis, night sweats, myalgia, arthralgia, pain in extremity, malaise, and asthenia but are still considered adverse reactions for this age group.

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

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Table B-6. ADRs by SOC and CIOMS Frequency Category* Listed in Order of Decreasing Medical Seriousness Within Each Frequency Category and SOC: BNT162b2-Experienced Individuals (18 to 55 Years of Age) Who Were Rerandomized to Receive 1 Booster (Dose 3) of BNT162b2 (30 µg) – Booster Safety Population (17 June 2021 Data Cut-off Date)†,[64]

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

* CIOMS frequency categories are based on clinical trial C4591001 crude incidence and was reported to only one significant figure.

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

a. These adverse reactions were identified in the post-authorization period. The following events were not reported in the booster safety population in Study C4591001: angioedema, pruritus, urticaria, malaise, lethargy, asthenia, hyperhidrosis, and night sweats but are still considered adverse reactions for this age group.

b. The following event is categorized as a hypersensitivity reaction: rash.

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Table B-7. Non-reactogenicity* ADRs by System Organ Class and CIOMS Frequency Category† Listed in Order of Decreasing Medical Seriousness Within Each Frequency Category and System Organ Class: Study C4591031 Substudy A (SSA), Individuals ≥16 Years of Age who Received 1 Booster (Dose 3) of BNT162b2 (30 µg) in Study C4591031 SSA (5 October 2021 Data Cut-off Date)[64]

System Organ Class	Very Common ≥1/10 (≥10%)	Common ≥1/100 to <1/10 (≥1% to <10%)	Uncommon ≥1/1,000 to <1/100 (≥0.1% to <1%)	Rare ≥1/10,000 to <1/1,000 (≥0.01% to <0.1%)	Very Rare <1/10,000 (<0.01%)	Frequency not known (cannot be estimated from the available data)
Blood and lymphatic system disorders		Lymphadenopathy				
Immune system disorders			Pruritus[a,b]; Rash[a,b]	Urticaria[a,b]		Anaphylaxis[a]
Metabolism and nutrition disorders			Decreased appetite			
Nervous system disorders			Lethargy			
Cardiac disorders					Myocarditis[a]; Pericarditis[a]	
Gastrointestinal disorders			Nausea			
Skin and subcutaneous tissue disorders			Hyperhidrosis; Night sweats			
Musculoskeletal and connective tissue disorders		Pain in extremity (arm)[a]				
General disorders and administration site conditions			Asthenia; Malaise			

* Please see Table A-6 and Table B-6 for the frequencies and CIOMS Frequency Categories for the following reactogenicity adverse reactions that were reported in the booster safety population of Study C4591001: headache, diarrhea, vomiting, myalgia (muscle pain), arthralgia (joint pain) (new), injection site pain, fatigue, chills, pyrexia, injection site swelling, injection site redness.

† CIOMS frequency categories are based on clinical trial C4591031 crude incidence and was reported to only one significant figure.

Please see Table B-6 for the CIOMS Frequency Categories for the following reactogenicity adverse reactions that were reported in the booster safety population of Study C4591001: headache, diarrhea, vomiting, myalgia (muscle pain), arthralgia (joint pain) (new), injection site pain, fatigue, chills, pyrexia, injection site swelling, injection site redness.

The preferred term pyrexia is a cluster term also covering 'body temperature increased'.

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

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

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Table B-8. ADRs by System Organ Class and CIOMS Frequency Category* Listed in order of Decreasing Medical Seriousness Within Each Frequency Category and System Organ Class: Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency Within Each System Organ Class: Individuals 18 to 55 years old Who Received a Booster (Dose 4) of BNT162b2 30 µg in Study C4591031 Substudy D (SSD) — Safety Population (11 March 2022 Data Cut-off Date)[64]

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

* CIOMS frequency categories are based on clinical trial C4591031 SSD crude incidence and was reported to only one significant figure.

a. These adverse reactions were identified in the post-authorization period. At the time of the data cut-off date, the following reactions were not reported in the safety population in Study C4591031 SSD: rash, pruritus, urticaria, angioedema, decreased appetite, lethargy, nausea, hyperhidrosis, night sweats, pain in extremity, malaise, and asthenia but are still considered adverse reactions.

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Table B-9. ADRs by System Organ Class and CIOMS Frequency Category* Listed in Order of Decreasing Medical Seriousness Within Each Frequency Category and System Organ Class: Individuals >55 years old Who Received a Booster (Dose 4) of BNT162b2 30 µg in Study C4591031 Substudy E (SSE) – Expanded Cohort – Safety Population (16 May 2022 Data Cut-off Date)[64]

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

* CIOMS frequency categories are based on clinical trial C4591031 SSE crude incidence and was reported to only one significant figure.

a. These adverse reactions were identified in the post-authorization period. At the time of the data cut-off date, the following reactions were not reported in the safety population in Study C4591031 SSE: rash, pruritus, urticaria, angioedema, decreased appetite, lethargy, hyperhidrosis, night sweats, malaise and asthenia but are still considered adverse reactions.

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Table B-10. ADRs by System Organ Class and CIOMS Frequency Category* Listed in Order of Decreasing Medical Seriousness Within Each Frequency Category and System Organ Class: Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency Within Each System Organ Class: Individuals 18 to 55 Years Old Who Received a Booster (Dose 4) of Monovalent BNT162b2 OMI BA.1 (30 µg) in Study C4591031 Substudy D (SSD) — Safety Population (11 March 2022 Data Cut-off Date)[64]

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

* CIOMS frequency categories are based on clinical trial C4591031 SSD crude incidence and was reported to only one significant figure.

a. These adverse reactions were identified in the post-authorization period. At the time of the data cut-off date, the following reactions were not reported in the safety population in Study C4591031 SSD: rash, pruritus, urticaria, angioedema, decreased appetite, lethargy, nausea, hyperhidrosis, pain in extremity, malaise, and asthenia but are still considered adverse reactions.

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Table B-11. ADRs by System Organ Class and CIOMS Frequency Category* Listed in order of Decreasing Medical Seriousness Within Each Frequency Category and System Organ Class: Individuals >55 years old Who Received a Booster (Dose 4) of Bivalent BNT162b2 (15 µg) + BNT162b2 OMI BA.1 (15 µg) in Study C4591031 Substudy E (SSE) – Expanded Cohort – Safety Population (16 May 2022 Data Cut-off Date)[64]

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

* CIOMS frequency categories are based on clinical trial C4591031 SSE crude incidence and was reported to only one significant figure.
a. These adverse reactions were identified in the post-authorization period. At the time of the data cut-off date, the following reactions were not reported in the safety population in Study C4591031 SSE: rash, pruritus, urticaria, angioedema, decreased appetite, lethargy, hyperhidrosis, night sweats, pain in extremity and asthenia but are still considered adverse reactions.

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Table B-12. ADRs by System Organ Class and CIOMS Frequency Category* Listed in Order of Decreasing Medical Seriousness Within Each Frequency Category and System Organ Class: Individuals 5 Through <12 Years of Age Who Received Dose 3 (22 March 2022 Data Cut-off Date)[†,64,84]

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

* CIOMS frequency categories are based on clinical trial C4591007 crude incidence and was reported to only one significant figure.

† Dose 3 (a booster dose) of BNT162b2 10 µg was administered to participants 5 through <12 years of age in Study C4591007.

a. These adverse reactions were identified in the post-authorization period. At the time of the data cut-off date, the following reactions were not reported in participants 5 through <12 years of age in Study C4591007 after Dose 3: urticaria, pruritus, angioedema, decreased appetite, lethargy, myocarditis, pericarditis, nausea, night sweats, hyperhidrosis, pain in extremity (arm), malaise, and asthenia but are still considered adverse reactions in this age group.

b. The following event is categorized as a hypersensitivity reaction: rash.

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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.

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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

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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 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.

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PREPARED BY PFIZER INC

CDS EFFECTIVE DATE: 8-SEP-2022

Date of Superseded CDS: 31-Aug-2022

COVID-19 mRNA Vaccine

CORE DATA SHEET

VERSION 16

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1. NAME OF THE MEDICINAL PRODUCT

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

{{COMIRNATY Bivalent Original and Omicron BA.1 15/15 micrograms per dose is called TRADENAME (Bivalent)}}.

{{COMIRNATY Bivalent Original and Omicron BA.4/BA.5 15/15 micrograms per dose is called TRADENAME (Bivalent)}}.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION[1,2,72,85,120]

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

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

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

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

For the full list of excipients, see Section 6.1.

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

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

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

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

For the full list of excipients, see Section 6.1.

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

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

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

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

For the full list of excipients, see Section 6.1.

*[Editorial guidance for countries: Select this text for the **Tris/Sucrose presentation, 3 micrograms/dose**.]*

TRADENAME (for age 6 months to <5 years): This is a multidose vial and must be diluted before use. One vial (0.4 mL) contains 10 doses of 0.2 mL after dilution (see Sections 4.2 and 6.6).

One dose (0.2 mL) contains 3 micrograms of COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

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

For the full list of excipients, see Section 6.1.

*[Editorial guidance for countries: Select this text for the **Bivalent (Original/Omicron) presentation, 15/15 micrograms/dose**.]*

TRADENAME (Bivalent): This is a multidose vial. One vial (2.25 mL) contains 6 doses of 0.3 mL (see Sections 4.2 and 6.6).

One dose (0.3 mL) contains 15/15 micrograms of COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

TRADENAME (Bivalent) 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) (Original and {{Omicron BA.1}} {{Omicron BA.4/BA.5}}).

For the full list of excipients, see Section 6.1.

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3. PHARMACEUTICAL FORM[2,3,72,85]

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

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

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

TRADENAME (Do Not Dilute): Dispersion for injection.

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

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

*[Editorial guidance for countries: Select this text for the **Tris/Sucrose presentation, 3 micrograms/dose**.]*

TRADENAME (for age 6 months to <5 years): Concentrate for dispersion for injection.

*[Editorial guidance for countries: Select this text for the **Bivalent (Original/Omicron) presentation, 15/15 micrograms/dose**.]*

TRADENAME (Bivalent): Dispersion for injection.

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

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

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

Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 virus, in individuals 6 months of age and older.[4,49,73,86]

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4.2. Posology and method of administration

Posology

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

Individuals 12 years of age and older

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

Booster dose in individuals 12 years of age and older

A booster dose of TRADENAME (Dilute Before Use) or TRADENAME (Do Not Dilute) may be administered intramuscularly at least 5 months after the second dose in individuals 12 years of age and older.[71,87]

Subsequent doses of TRADENAME (Dilute Before Use) or TRADENAME (Do Not Dilute) may be administered to individuals 12 years of age and older at least 4 months after a previous booster dose of TRADENAME.[121]

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

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

Interchangeability

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

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

For further information on efficacy, see Section 5.1.

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

Individuals 5 through <12 years of age

TRADENAME (for age 5 years to <12 years) is administered intramuscularly after dilution as a primary series of 2 doses (0.2 mL) at greater than or equal to 21 days (preferably 3 weeks) apart.[73]

Booster dose in individuals 5 through <12 years of age

A booster dose of TRADENAME (for age 5 years to <12 years of age) may be administered intramuscularly at least 6 months after the second dose in individuals 5 years through <12 years of age.[84]

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

Interchangeability

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

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

For further information on efficacy, see Section 5.1.

*[Editorial guidance for countries: Select this text for the **Tris/Sucrose presentation, 3 micrograms/dose**.]*

Individuals 6 months through <5 years of age

TRADENAME (for age 6 months to <5 years) is administered intramuscularly after dilution as a primary series of 3 doses (0.2 mL). The initial 2 doses are administered 3 weeks apart followed by a third dose administered at least 8 weeks after the second dose.[86]

Individuals who will turn from 4 years to 5 years of age between their doses in the vaccination series should receive their age-appropriate dose at the time of the vaccination and the interval between doses is determined by the individual's age at the start of the vaccination series.[88]

TRADENAME (for age 6 months to <5 years) cannot be used in individuals 5 years of age and older.

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Interchangeability

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

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

For further information on efficacy, see Section 5.1.

*[Editorial guidance for countries: Select this text for the **Bivalent (Original/Omicron) presentation, 15/15 micrograms/dose**.]*

Booster dose in individuals 12 years of age and older

A booster dose of TRADENAME (Bivalent) may be administered intramuscularly at least 5 months after completing the primary series of TRADENAME. Subsequent doses of TRADENAME (Bivalent) may be administered to individuals 12 years of age and older at least 4 months after a previous booster dose of TRADENAME or TRADENAME (Bivalent).

For further information on efficacy, see Section 5.1.

Pediatric population

The safety and efficacy of TRADENAME in individuals under 6 months of age have not yet been established. The safety and effectiveness of a booster dose of TRADENAME in individuals 16 through 17 years of age is based on safety and effectiveness data in adults at least 18 through 55 years of age.[71,86]

{{The safety and efficacy of TRADENAME (Bivalent) in children less than 12 years of age has 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]

The safety of a booster dose of TRADENAME in individuals 65 years of age and older is based on safety data in 12 booster dose recipients 65 through 85 years of age in Study 2, 306 booster dose recipients 18 through 55 years of age in Study 2, and 1,175 booster dose recipients 65 years of age and older in Study 4. The effectiveness of a booster dose of TRADENAME in individuals 65 years of age and older is based on effectiveness data in 306 booster dose recipients 18 through

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55 years of age in Study 2, and an efficacy analysis from participants 16 years of age and older in 9,945 participants in Study 4.[71, 80]

Method of administration

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

Administer TRADENAME intramuscularly in the deltoid muscle.

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

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

Individuals 12 years of age and older

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

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

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

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

Administer TRADENAME intramuscularly in the deltoid muscle.

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

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

Individuals 12 years of age and older

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

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

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

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

Administer TRADENAME intramuscularly in the deltoid muscle.

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

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

Individuals 5 through <12 years of age

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

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

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

*[Editorial guidance for countries: Select this text for the **Tris/Sucrose presentation, 3 micrograms/dose**.]*

In individuals 6 to less than 12 months of age, administer TRADENAME intramuscularly in the anterolateral aspect of the thigh. In individuals 1 years of age and older, administer TRADENAME intramuscularly in the anterolateral aspect of the thigh or the deltoid muscle.

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

After dilution, vials of TRADENAME (for age 6 months to <5 years) contains 10 doses of 0.2 mL of vaccine.

Individuals 6 months through <5 years of age

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

- Each dose must contain 0.2 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.2 mL, discard the vial and content.

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- Do not pool excess vaccine from multiple vials.

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

*[Editorial guidance for countries: Select this text for the **Bivalent (Original/Omicron) presentation, 15/15 micrograms/dose**.]*

Administer TRADENAME (Bivalent) intramuscularly in the deltoid muscle.

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

Vials of TRADENAME (Bivalent) contain 6 doses of 0.3 mL of vaccine.

Individuals 12 years of age and older

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

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

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

4.3. Contraindications

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

4.4. Special warnings and precautions for use

Traceability

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

General recommendations

As with all injectable vaccines, appropriate medical treatment and supervision must always be readily available in case of a rare anaphylactic event following the administration of the vaccine.[9]

Very rare cases of myocarditis and pericarditis have been reported following vaccination with TRADENAME. Typically, the cases have occurred more often in younger men and after the second dose of the vaccine and within 14 days after vaccination. Based on accumulating data, the

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reporting rates of myocarditis and pericarditis after primary series in children ages 5 through <12 years are lower than in ages 12 through 17 years. Rates of myocarditis and pericarditis in booster doses do not appear to be higher than after the second dose in the primary series. The cases are generally mild and individuals tend to recover within a short time following standard treatment and rest. Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis in vaccine recipients.[69,89]

The administration of TRADENAME {{or TRADENAME (Bivalent)}} 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 {{or TRADENAME (Bivalent)}} 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 {{or TRADENAME (Bivalent)}} 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.

{{No data are available yet regarding the use of TRADENAME (Bivalent) during pregnancy.}}

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Lactation

It is unknown whether TRADENAME is excreted in human milk.

{{No data are available yet regarding the use of TRADENAME (Bivalent) during breast-feeding.}}

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]

{{It is unknown whether TRADENAME (Bivalent) has an impact on fertility.}}

4.7. Effects on ability to drive and use machines

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

4.8. Undesirable effects

Summary of safety profile

The safety of TRADENAME was evaluated in participants 5 years of age and older in 3 clinical studies conducted in the United States, Europe, Turkey, South Africa, and South America.[12,49] Study BNT162-01 (Study 1) enrolled 60 participants, 18 through 55 years of age and 36 participants, 56 through 85 years of age.[68] Study C4591001 (Study 2) enrolled approximately 46,000 participants,[41] 12 years of age or older.[12] Study C4591007 (Study 3) enrolled approximately 2,300 participants 5 through <12 years of age.[73] Study 3 also enrolled approximately 1,800 participants 2 through 4 years of age and 1,200 participants 6 months through 23 months of age.[86]

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

In Study C4591031 (Study 4), a placebo-controlled booster study, 5,081 participants 16 years of age and older were recruited from Study 2 to receive a booster dose of TRADENAME at least 6 months after the second dose. The overall safety profile for the booster dose was similar to that seen after 2 doses.[80]

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In a subset of Study 3 (Phase 2/3) participants, 401 participants 5 through <12 years of age received a booster dose of TRADENAME at least 5 months after completing the primary series. The overall safety profile for the booster dose was similar to that seen after the primary series.[84]

Participants 16 years of age and older – after 2 doses

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

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

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

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

Adolescents 12 through 15 years of age – after 2 doses[81]

In an analysis of long-term safety follow-up in Study 2, 2,260 adolescents (1,131 TRADENAME; 1,129 placebo) were 12 through 15 years of age. Of these, 1,559 adolescents (786 TRADENAME and 773 placebo) have been followed for ≥4 months after the second dose.[41,42] The safety evaluation in Study 2 is ongoing.

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

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

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

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

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Children 2 through 4 years of age – after 3 doses[90,91,92]

In an analysis of Study 3 (Phase 2/3), 2,750 individuals (1,835 TRADENAME 3 mcg and 915 placebo) were 2 through 4 years age. Based on data in the blinded placebo-controlled follow-up period up to the cutoff date of April 29, 2022, 886 individuals 2 through 4 years of age who received a 3-dose primary course (606 TRADENAME 3 mcg and 280 placebo) have been followed a median of 1.4 months after the third dose.

The most frequent adverse reactions in children 2 through 4 years of age that received any primary series dose included pain at injection site and fatigue (>40%), injection site redness and fever (>10%).

Children 6 through 23 months of age – after 3 doses[93,94,95]

In an analysis of Study 3 (Phase 2/3), 1,776 individuals (1,178 TRADENAME 3 mcg and 598 placebo) were 6 through 23 months of age. Based on data in the blinded placebo-controlled follow-up period up to the cutoff date of April 29, 2022, 570 individuals 6 through 23 months of age who received a 3-dose primary course (386 TRADENAME 3 mcg and 184 placebo) have been followed for a median of 1.3 months after the third dose.

The most frequent adverse reactions in children 6 through 23 months of age that received any primary series dose included irritability (>60%), decrease appetite (>30%), tenderness at the injection site (>20%), injection site redness and fever (>10%).

Participants 12 years of age and older – after booster dose[71]

The safety of a booster dose of TRADENAME in participants 12 years of age and older is inferred from safety data from studies of a booster dose of TRADENAME in participants 16 years of age and older.

A subset from Study 2 (Phase 2/3) participants of 306 adults at least 18 through 55 years of age who completed the primary TRADENAME 2-dose course, received a booster dose of TRADENAME approximately 6 months (range of 4.8 to 8.0 months) after receiving Dose 2. Of these, 301 participants have been followed for ≥4 months after the booster dose of TRADENAME.[96]

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

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In Study 4, a placebo-controlled booster study, participants 16 years of age and older recruited from Study 2 received a booster dose of TRADENAME (5,081 participants), or placebo (5,044 participants) at least 6 months after the second dose of TRADENAME. Overall, participants who received a booster dose, had a median follow-up time of 2.8 months (range 0.3 to 7.5 months) after the booster dose in the blinded placebo-controlled follow-up period to the cut-off date (8 February 2022).[80,97] Of these, 1281 participants (895 TRADENAME and 386 placebo) have been followed for ≥4 months after the booster dose of TRADENAME.[98]

Participants 12 years of age and older – after subsequent booster doses

The safety of a booster dose of TRADENAME in participants 12 years of age and older is inferred from safety data from studies of a booster dose of TRADENAME in participants 18 years of age and older.

A subset of 325 adults 18 to ≤55 years of age who had completed 3 doses of TRADENAME, received a booster (fourth dose) of TRADENAME (30 mcg) 90 to 180 days after receiving Dose 3.[122,123] Participants who received a booster (fourth dose) of TRADENAME (30 mcg) had a median follow-up time of 1.4 months.[124] The most frequent adverse reactions in these participants were injection site pain (>70%), fatigue (>60%), headache (>40%), myalgia and chills (>20%) and arthralgia (>10%).[125,126]

In a subset from Study 4 (Phase 3), 305 adults greater than 55 years of age who had completed 3 doses of TRADENAME, received a booster (fourth dose) of TRADENAME (30 mcg) 5.3 to 13.1 months after receiving Dose 3.[127,128] Participants who received a booster (fourth dose) of TRADENAME (30 mcg) had a median follow-up time of at least 1.7 months up to a data cutoff date of 16 May 2022.[129] The most frequent adverse reactions in participants greater than 55 years of age were injection site pain (>60%), fatigue (>40%), headache (>20%), myalgia and chills (>10%).[130,131,132]

Omicron-adapted TRADENAME – after a booster dose of TRADENAME (Bivalent, Original/Omicron BA.1) or monovalent Omicron BA.1 (fourth dose)

The safety of a booster dose of TRADENAME (Bivalent) in participants 12 years of age and older is inferred from safety data from studies of a booster dose of TRADENAME (Bivalent Original/Omicron BA.1) in individuals greater than 55 years of age and also safety data from studies of a booster dose of monovalent Omicron BA.1 in individuals 18 to ≤55 years of age.

Participants greater than 55 years of age – after a booster dose of TRADENAME (Bivalent, Original/Omicron BA.1)

In a subset from Study 4 (Phase 3), 305 adults greater than 55 years of age who had completed 3 doses of TRADENAME, received a booster (fourth dose) of TRADENAME (Bivalent, Original/Omicron BA.1) 15/15 mcg 4.7 to 11.5 months after receiving Dose 3.[133,134,135] Participants who received a booster (fourth dose) of TRADENAME (Bivalent, Original/Omicron BA.1) had a median follow-up time of at least 1.7 months up to a data cutoff date of 16 May 2022.[136,137]

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The overall safety profile for the TRADENAME (Bivalent, Original/Omicron BA.1) booster (fourth dose) was similar to that seen after the TRADENAME booster (third dose). The most frequent adverse reactions in participants greater than 55 years of age were injection site pain (>50%), fatigue (>40%), headache (>30%), myalgia (>20%), chills and arthralgia (>10%). No new adverse reactions were identified for TRADENAME (Bivalent, Original/Omicron BA.1).[138,139]

Participants 18 to ≤55 years of age – after a booster dose of monovalent Omicron BA.1

A subset of 315 adults 18 to ≤55 years of age who had completed 3 doses of TRADENAME, received a booster (fourth dose) of Omicron BA.1 30 mcg (monovalent) 90 to 180 days after receiving Dose 3.[122,123] Participants who received a booster (fourth dose) of monovalent Omicron BA.1 had a median follow-up time of 1.4 months.[124] The most frequent adverse reactions in these participants were injection site pain (>70%), fatigue (>60%), headache (>40%), myalgia (>30%), chills (>30%) and arthralgia (>20%).[125,126]

Children 5 through <12 years of age – after booster dose[84]

In a subset from Study 3, a total of 401 children 5 through <12 years of age received a booster dose of TRADENAME 10 mcg at least 5 months (range of 5 to 9 months) after completing the primary series. The analysis of the Study 3 (Phase 2/3) subset is based on data up to the cut-off date of March 22, 2022 (median follow-up time of 1.3 months).

The most frequent adverse reactions in participants 5 through <12 years of age were injection site pain (>70%), fatigue (>40%), headache (>30%), myalgia, chills, injection site redness, and swelling (>10%).

The adverse reactions in the tables below apply to TRADENAME and TRADENAME (Bivalent) and all age groups unless specified otherwise.

Table 1. Adverse Drug Reactions (Clinical Trials)[13,14,16,64,80,86]

System Organ Class	Adverse Drug Reactions
Blood and lymphatic system disorders	Lymphadenopathy[a]
Metabolism and nutrition disorders	Decreased appetite
Psychiatric disorders	Irritability[c]
Nervous system disorders	Headache Lethargy
Gastrointestinal disorders	Nausea
Skin and subcutaneous tissue disorders	Hyperhidrosis Night sweats
Musculoskeletal and connective tissue disorders	Arthralgia Myalgia

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System Organ Class	Adverse Drug Reactions
General disorders and administration site conditions	Pyrexia[b] Chills Asthenia Malaise Fatigue Injection site pain Injection site tenderness[c] Injection site swelling Injection site redness

a. A higher frequency of lymphadenopathy was observed in participants 5 through <12 years of age in Study 3 (2.5% vs. 0.9%) and in participants 16 years of age and older in Study 4 (2.8% vs. 0.4%) receiving a booster dose compared to participants receiving 2 doses.[71,84]
b. A higher frequency of pyrexia was observed after the second dose compared to the first dose. The preferred term pyrexia is a cluster term covering also body temperature increased.
c. Irritability and injection site tenderness pertain to participants 6 through 23 months of age.[86]

Table 2. Adverse Drug Reactions (Post-authorization Experience)[38,64,80,89]

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

a. A higher frequency of pain in extremity (1.1% vs. 0.8%) was observed in participants receiving a booster dose in Study 4 compared to participants receiving 2 doses.

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.

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

Efficacy

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

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

In the Phase 2/3 portion of Study 2, based on data accrued through 14 November 2020, approximately 44,000 participants 12 years of age and older were randomized equally and received 2 doses of TRADENAME 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 TRADENAME 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.

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

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

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

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At the time of the primary efficacy analysis, participants had been followed for symptomatic COVID-19 for at least 2214 person-years for the TRADENAME 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]

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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.

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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.

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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.

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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)

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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 1,000 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.

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

Subgroup	TRADENAME N[a]=22,166 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=22,320 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]
Sex			
Male	44 3.376 (11,103)	411 3.181 (10,920)	89.9 (86.2, 92.8)
Female	37 3.133 (10,539)	462 3.093 (10,769)	92.1 (88.9, 94.5)
Ethnicity			
Hispanic or Latino	32 1.862 (5408)	245 1.794 (5391)	87.4 (81.8, 91.6)
Not Hispanic or Latino	48 4.615 (16,128)	628 4.445 (16,186)	92.6 (90.1, 94.6)
Race			
Black or African American	4 0.611 (1958)	49 0.601 (1985)	92.0 (78.1, 97.9)
White	69 5.379 (17,801)	768 5.191 (17,880)	91.3 (88.9, 93.3)
All others[f]	8 0.519 (1883)	56 0.481 (1824)	86.8 (72.1, 94.5)
Country			
Argentina	16 1.033 (2655)	110 1.017 (2670)	85.7 (75.7, 92.1)
Brazil	14 0.441 (1419)	82 0.408 (1401)	84.2 (71.9, 91.7)
Germany	0 0.047 (237)	1 0.048 (243)	100.0 (-3868.6, 100.0)
South Africa	0 0.099 (358)	10 0.096 (358)	100.0 (56.6, 100.0)
Turkey	0 0.029 (238)	6 0.026 (232)	100.0 (22.2, 100.0)
United States	51 4.861 (16,735)	664 4.678 (16,785)	92.6 (90.2, 94.6)

Notes: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting). Included confirmed cases in participants 12 through 15 years of age: 0 in the TRADENAME group; 18 in the placebo group.

* Participants who had no evidence of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

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a. N = Number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Two-sided confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
f. All others = American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported race categories.

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

Table 9. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – Participants Without Evidence of Infection* Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population[23]

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

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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 obese			
16 to 64 and not obese	4 1.107 (8811)	83 1.101 (8825)	95.2 (87.3, 98.7)
16 to 64 and obese	3 0.598 (4734)	60 0.609 (4789)	94.9 (84.4, 99.0)
≥65 and not obese	1 0.343 (2582)	12 0.338 (2567)	91.8 (44.5, 99.8)
≥65 and obese	0 0.165 (1265)	7 0.173 (1313)	100.0 (27.1, 100.0)

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

* Subjects who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

a. N = number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
f. At risk is defined as having at least 1 of the Charlson Comorbidity Index (CMI) category or obesity (BMI ≥30 kg/m^2).
g. Obese is defined as BMI ≥30 kg/m^2.

The updated subgroup analyses of vaccine efficacy by risk status in participants followed up to 6 months after Dose 2 (with a cut-off date of 13 March 2021) are presented in Table 10 and Table 11.

Table 10. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – Participants Without Evidence of Infection* Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period[55]

Subgroup	TRADENAME N[a]=20,998 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=21,096 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]
First COVID-19 occurrence from 7 days after Dose 2[f]	77 6.247 (20,712)	850 6.003 (20,713)	91.3 (89.0, 93.2)

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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]
At risk[g]			
Yes	35 2.797 (9167)	401 2.681 (9136)	91.6 (88.2, 94.3)
No	42 3.450 (11,545)	449 3.322 (11,577)	91.0 (87.6, 93.6)
Age group (years) and risk status			
16 through 64 and not at risk	41 2.776 (8887)	385 2.661 (8886)	89.8 (85.9, 92.8)
16 through 64 and at risk	29 2.083 (6632)	325 1.993 (6629)	91.5 (87.5, 94.4)
65 and older and not at risk	1 0.553 (1870)	53 0.546 (1922)	98.1 (89.2, 100.0)
65 and older and at risk	6 0.680 (2322)	71 0.656 (2304)	91.8 (81.4, 97.1)
Obese[h]			
Yes	27 2.103 (6796)	314 2.050 (6875)	91.6 (87.6, 94.6)
No	50 4.143 (13,911)	536 3.952 (13,833)	91.1 (88.1, 93.5)
Age group (years) and obesity status			
16 through 64 and not obese	46 3.178 (10,212)	444 3.028 (10,166)	90.1 (86.6, 92.9)
16 through 64 and obese	24 1.680 (5303)	266 1.624 (5344)	91.3 (86.7, 94.5)
65 and older and not obese	4 0.829 (2821)	79 0.793 (2800)	95.2 (87.1, 98.7)
65 and older and obese	3 0.404 (1370)	45 0.410 (1426)	93.2 (78.9, 98.7)

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Subgroup	TRADENAME N[a]=20,998 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=21,096 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]

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

* Participants who had no evidence of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

a. N = Number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Two-sided confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.
f. Included confirmed cases in participants 12 through 15 years of age: 0 in the TRADENAME group; 16 in the placebo group.
g. At risk is defined as having at least 1 of the Charlson Comorbidity Index (CMI) category or obesity (BMI ≥30 kg/m^2 or BMI ≥95th percentile [12 through 15 Years of age]).
h. Obese is defined as BMI ≥30 kg/m^2. For 12 through 15 years age group, obesity is defined as a BMI at or above the 95th percentile. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.

Table 11. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – Participants With or Without* Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period[56]

Subgroup	TRADENAME N[a]=22,166 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=22,320 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]
First COVID-19 occurrence from 7 days after Dose 2[f]	81 6.509 (21,642)	873 6.274 (21,689)	91.1 (88.8, 93.0)

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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]
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)

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.

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Subgroup	TRADENAME N[a]=22,166 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=22,320 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]

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

Efficacy against severe COVID-19 - after 2 doses

Secondary efficacy analyses suggested benefit of TRADENAME 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 TRADENAME group and 9 cases in placebo group), with an estimated vaccine efficacy of 75.0% (95% CI: -152.6, 99.5) (1 case in TRADENAME 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 TRADENAME 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)

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

Efficacy and immunogenicity in adolescents 12 to 15 years of age – after 2 doses

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

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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 through 25 years of age who had no serological or virological evidence of past SARS-CoV-2 infection. The immune response to TRADENAME in adolescents 12 to 15 years of age (n=190) was non-inferior to the immune

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response in participants 16 through 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 through 25 years of age group was 1.76, with a 2-sided 95% CI of 1.47 to 2.10, meeting the 1.5-fold non-inferiority criterion (the lower bound of the 2-sided 95% CI for the 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 through 25 years of age.[48]

An updated efficacy analysis of Study 2 has been performed in approximately 2,260 adolescents 12 through 15 years of age evaluating confirmed COVID-19 cases accrued up to a data cut-off date of September 2, 2021, representing up to 6 months of follow-up after Dose 2 for participants in the efficacy population.[81]

The updated vaccine efficacy information in adolescents 12 through 15 years of age is presented in Table 14.

Table 14. 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 Through 15 Years of Age Evaluable Efficacy (7 Days) Population[81]

First COVID-19 occurrence from 7 days after Dose 2 in adolescents 12 through 15 years of age without evidence of prior SARS-CoV-2 infection*			
	TRADENAME N[a]=1057 Cases n1[b] Surveillance Time[c] (n2[d])	**Placebo N[a]=1030 Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI[e])**
Adolescents 12 through 15 years of age	0 0.343 (1043)	28 0.322 (1019)	100.0 (86.8, 100.0)
First COVID-19 occurrence from 7 days after Dose 2 in adolescents 12 through 15 years of age with or without evidence of prior SARS-CoV-2 infection			
	TRADENAME N[a]=1119 Cases n1[b] Surveillance Time[c] (n2[d])	**Placebo N[a]=1109 Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI[e])**
Adolescents 12 through 15 years of age	0 0.362 (1098)	30 0.345 (1088)	100.0 (87.5, 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).

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* 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.

Efficacy in children 5 through <12 years of age – after 2 doses

A descriptive efficacy analysis of Study 3 has been performed in 1,968 children 5 through <12 years of age without evidence of infection prior to 7 days after Dose 2. This analysis evaluated confirmed symptomatic COVID-19 cases accrued up to a data cut-off date of October 8, 2021.[82]

Table 15 presents the specific demographic characteristics in participants who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose.

Table 15. Demographics Characteristics – Participants Without Evidence of Infection Prior to 7 Days After Dose 2 – Phase 2/3 – 5 Through <12 Years of Age – Evaluable Efficacy Population[82]

	TRADENAME 10 mcg/dose (N[a]=1305) n[b] (%)	**Placebo (N[a]=663) n[b] (%)**
Sex		
Male	679 (52.0)	343 (51.7)
Female	626 (48.0)	320 (48.3)
Age at Vaccination		
Mean (SD)	8.2 (1.93)	8.1 (1.98)
Median	8.0	8.0
Min, max	(5, 11)	(5, 11)
Race		
White	1018 (78.0)	514 (77.5)
Black or African American	76 (5.8)	48 (7.2)
American Indian or Alaska Native	<1.0%	<1.0%
Asian	86 (6.6)	46 (6.9)
Native Hawaiian or other Pacific Islander	<1.0%	<1.0%
Other[c]	110 (8.4)	52 (7.8)

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	TRADENAME 10 mcg/dose (N[a]=1305) n[b] (%)	Placebo (N[a]=663) n[b] (%)
Ethnicity		
Hispanic or Latino	243 (18.6)	130 (19.6)
Not Hispanic or Latino	1059 (81.1)	533 (80.4)
Not reported	<1.0%	<1.0%
Comorbidities[d]		
Yes	262 (20.1)	133 (20.1)
No	1043 (79.9)	530 (79.9)

a. N = number of participants in the specified group from the evaluable efficacy population with no evidence of SARS CoV-2 infection prior to 7 days after Dose 2. This value is the denominator for the percentage calculations. Evaluable efficacy population included all eligible randomized participants who received all vaccination(s) as randomized within the predefined window, had no other important protocol deviations as determined by the clinician.
b. n = Number of participants with the specified characteristic.
c. Includes multiracial and not reported.
d. Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as participants who had at least 1 of the prespecified comorbidities based on MMWR 69(32);1081-1088 and/or obesity (BMI ≥95th percentile).

The descriptive vaccine efficacy results in children 5 through <12 years of age without evidence of prior SARS-CoV-2 infection are presented in Table 16. None of the cases accrued met criteria for severe COVID-19 or multisystem inflammatory syndrome in children (MIS-C). No cases of COVID-19 were observed in either the vaccine group or the placebo group in participants with evidence of prior SARS-CoV-2 infection.[82]

Table 16. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2: Without Evidence of Infection Prior to 7 Days After Dose 2 – Phase 2/3 – Children 5 Through <12 Years of Age Evaluable Efficacy Population[82]

First COVID-19 occurrence from 7 days after Dose 2 in children 5 through <12 years of age without evidence of prior SARS-CoV-2 infection*			
	TRADENAME 10 mcg/dose N[a]=1305 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=663 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)
Children 5 through 11 years of age	3 0.322 (1273)	16 0.159 (637)	90.7 (67.7, 98.3)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting).
* Participants who had no evidence of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
a. N = Number of participants in the specified group.

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b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1,000 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.

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

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

In Study 3, an analysis of SARS-CoV-2 50% neutralizing titers (NT50) 1 month after Dose 2 in a randomly selected subset of participants demonstrated effectiveness by immunobridging of immune responses comparing children 5 through <12 years of age in the Phase 2/3 part of Study 3 to participants 16 through 25 years of age in the Phase 2/3 part of Study 2 who had no serological or virological evidence of past SARSCoV-2 infection up to 1 month after Dose 2, meeting the prespecified immunobridging criteria for both the GMR and the seroresponse difference with seroresponse defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from baseline (before Dose 1).

The ratio of the SARS-CoV-2 NT50 in children 5 through <12 years of age to that of young adults 16 through 25 years of age was 1.04 (2-sided 95% CI: 0.93, 1.18), as presented in Table 17.

Table 17. Summary of Geometric Mean Ratio for 50% Neutralizing Titer – Comparison of Children 5 Through <12 Years of Age (Study 3) to Participants 16 Through 25 Years of Age (Study 2) – Participants Without* Evidence of Infection up to 1 Month After Dose 2 – Dose 2 Evaluable Immunogenicity Population[73]

		TRADENAME			
		10 mcg/Dose 5 Through <12 Years n^a=264	30 mcg/Dose 16 Through 25 Years n^a=253	5 Through <12 Years/ 16 Through 25 Years	
Assay	Time Point[b]	GMT[c] (95% CI[c])	GMT[c] (95% CI[c])	GMR[d] (95% CI[d])	Met Immunobridging Objective[e] (Y/N)
SARS-CoV-2 neutralization assay - NT50 (titer)[f]	1 month after Dose 2	1197.6 (1106.1, 1296.6)	1146.5 (1045.5, 1257.2)	1.04 (0.93, 1.18)	Y

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

* Participants who had no serological or virological evidence (up to 1 month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and 1 month after Dose 2, SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT (nasal swab) at any

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unscheduled visit up to 1 month after Dose 2 blood collection) and had no medical history of COVID-19 were included in the analysis.

a. n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
b. Protocol-specified timing for blood sample collection.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
d. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titers (Group 1[5 through <12 years of age] - Group 2 [16 through 25 years of age]) and the corresponding CI (based on the Student t distribution).
e. Immunobridging is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥0.8.
f. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, 99.2% of children 5 through <12 years of age and 99.2% of participants 16 through 25 years of age had a seroresponse from before vaccination to 1 month after Dose 2. The difference in proportions of participants who had seroresponse between the 2 age groups (children – young adult) was 0.0% (2-sided 95% CI: -2.0%, 2.2%), as presented in Table 18.

Table 18. Difference in Percentages of Participants With Seroresponse – Participants Without* Evidence of Infection up to 1 Month After Dose 2 – Immunobridging Subset – Phase 2/3 – Comparison of 5 Through <12 Years of Age to Study 2 Phase 2/3 16 Through 25 Years of Age – Evaluable Immunogenicity Population[73]

		TRADENAME			
		Study 3 10 mcg/Dose 5 Through <12 Years N[a]=264	Study 2 30 mcg/Dose 16 Through 25 Years N[a]=253	5 Through <12 Years / 16 Through 25 Years	
Assay	Time Point[b]	n[c] (%) (95% CI[d])	n[c] (%) (95% CI[d])	Difference %[e] (95% CI[f])	Met Immunobridging Objective[g] (Y/N)
SARS-CoV-2 neutralization assay - NT50 (titer)[h]	1 month after Dose 2	262 (99.2) (97.3, 99.9)	251 (99.2) (97.2, 99.9)	0.0 (-2.0, 2.2)	Y

Abbreviations: LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer 50; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result ≥4 × LLOQ is considered a seroresponse.

* Participants who had no serological or virological evidence (up to 1 month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and 1 month after Dose 2, SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT (nasal swab) at any unscheduled visit up to 1 month after Dose 2 blood collection) and had no medical history of COVID-19 were included in the analysis.

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a. N = number of participants with valid and determinate assay results both before vaccination and at 1 month after Dose 2. These values are the denominators for the percentage calculations.
b. Protocol-specified timing for blood sample collection.
c. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.
d. Exact 2-sided CI based on the Clopper and Pearson method.
e. Difference in proportions, expressed as a percentage (Group 1 [5 through <12 years of age] – Group 2 [16 through 25 years of age]).
f. 2-Sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
g. Immunobridging is declared if the lower bound of the 2-sided 95% CI for the difference in proportions is greater than -10.0%.
h. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

Efficacy and immunogenicity in individuals 6 months through <5 years of age – 3-dose primary course[86]

A descriptive efficacy analysis was performed across the combined population of participants 6 months through <5 years of age based on cases confirmed among 992 participants in the TRADENAME group and 464 participants in the placebo group who received all 3 doses of study intervention during the blinded follow-up period. The observed vaccine efficacy from at least 7 days after Dose 3 to the cutoff date (29 April 2022) was 80.3% (2-sided 95% CI: 13.9, 96.7) based on 3 cases in the TRADENAME group and 7 cases in the placebo group, adjusted for surveillance time (noting 2:1 randomization ratio).

Children 2 through 4 years of age – after 3 doses[86]

A descriptive efficacy analysis of Study 3 has been performed in participants 2 through 4 years of age. This analysis evaluated confirmed symptomatic COVID-19 cases accrued up to a data cutoff date of 29 April 2022.

Table 19 presents the specific demographic characteristics in participants 2 through 4 years of age who received 3 doses of TRADENAME (3 mcg modRNA) or placebo.

Table 19. Demographics Characteristics – Phase 2/3 – Participants 2 Through 4 Years of Age – Dose 3 All-Available Efficacy Population[99]

	TRADENAME 3 mcg/Dose (N[a]=606) n[b] (%)	**Placebo (N[a]=280) n[b] (%)**
Sex		
Male	290 (47.9)	124 (44.3)
Female	316 (52.1)	156 (55.7)

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	TRADENAME 3 mcg/Dose (N[a]=606) n[b] (%)	**Placebo (N[a]=280) n[b] (%)**
Age at Vaccination (years)		
Mean (SD)	2.9 (0.77)	2.9 (0.75)
Median	3.0	3.0
Min, max	(2, 4)	(2, 4)
Race		
White	455 (75.1)	219 (78.2)
Black or African American	29 (4.8)	13 (4.6)
American Indian or Alaska Native	0	2 (0.7)
Asian	64 (10.6)	26 (9.3)
Native Hawaiian or other Pacific Islander	1 (0.2)	0
Other[c]	57 (9.4)	20 (7.1)
Ethnicity		
Hispanic or Latino	77 (12.7)	36 (12.9)
Not Hispanic or Latino	528 (87.1)	244 (87.1)
Not reported	1 (0.2)	0
Comorbidities[d]		
Yes	71 (11.7)	42 (15.0)
No	535 (88.3)	238 (85.0)

Abbreviations: BMI = body mass, SD = standard deviation.

a. N = Number of participants in the specified group from the Dose 3 all-available efficacy population. This value is the denominator for the percentage calculations. Dose 3 all-available efficacy population included all randomized participants who received 3 doses of TRADENAME (3 mcg modRNA) or placebo.
b. n = Number of participants with the specified characteristic.
c. Includes multiracial and not reported.
d. Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as participants who had at least 1 of the prespecified comorbidities based on Morbidity and Mortality Weekly Report 69(32);1081-1088 and/or obesity (BMI ≥95th percentile).

The descriptive vaccine efficacy results after Dose 3 in participants 2 through 4 years of age are presented in Table 20.

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Table 20. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 3 - Phase 2/3 – Participants 2 Through 4 Years of Age – Dose 3 All-available Efficacy Population (Blinded Follow-up Period)[100]

	TRADENAME 3 mcg/Dose N[a]=606 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=280 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy (%) (95% CI[e])
First COVID-19 occurrence from 7 days after Dose 3	2 0.056 (481)	5 0.025 (209)	82.3 (-8.0, 98.3)

Abbreviation: VE = vaccine efficacy.

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; inability to eat/poor feeding).

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 3 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Two-sided 95% confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.

Additional evaluation of vaccine efficacy for cases confirmed at least 7 days after Dose 2 and before Dose 3 was performed. In the evaluable efficacy population in participants without prior evidence of SARS-CoV-2 infection before or during the vaccination regimen the observed vaccine efficacy from at least 7 days after Dose 2 and before Dose 3 was 35.9% (2-sided 95% CI: 11.0%, 53.7%). The vaccine efficacy in participants with or without prior evidence of SARS-CoV-2 infection before or during the vaccination regimen was similar.

Analysis of COVID-19 cases that excluded those involving coinfection with other respiratory pathogens did not meaningfully impact the estimated vaccine efficacy in this population.

Severe COVID-19 criteria (as described in the protocol, based on FDA definition and modified for children) were fulfilled for 7 cases (6 TRADENAME and 1 placebo) among participants 2 through 4 years of age, of which 5 of the 6 cases in the TRADENAME group fulfilled a single criterion of increased heart rate or respiratory rate and 1 case in the placebo group fulfilled a single criterion of decreased peripheral oxygen saturation (88% on room air). None of the cases accrued met criteria for multisystem inflammatory syndrome in children (MIS-C).

Immunogenicity analyses have been performed in the immunobridging subset of 143 Study 3 participants 2 through 4 years of age without evidence of infection up to 1 month after Dose 3 based on a data cutoff date of 29 April 2022.

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Table 21 presents the specific demographic characteristics in the studied evaluable immunogenicity population.

Table 21. Demographics Characteristics – Immunobridging Subset – Participants 2 Through 4 Years of Age (Study 3) and Participants 16 Through 25 Years of Age (Study 2) – Without Evidence of Infection -Evaluable Immunogenicity Population[101]

	TRADENAME 3 mcg/Dose 2 Through 4 Years of Age (N[a]=143) n[b] (%)	TRADENAME 30 mcg/Dose 16 Through 25 Years of Age (N[a]=170) n[b] (%)
Sex		
Male	63 (44.1)	79 (46.5)
Female	80 (55.9)	91 (53.5)
Age at Vaccination (years)		
Mean (SD)	2.7 (0.76)	21.2 (2.95)
Median	3.0	2.0
Min, max	(2, 4)	(16, 25)
Race		
White	99 (69.2)	130 (76.5)
Black or African American	8 (5.6)	15 (8.8)
American Indian or Alaska Native	0	3 (1.8)
Asian	16 (11.2)	13 (7.6)
Native Hawaiian or other Pacific Islander	0	1 (0.6)
Other[c]	20 (14.0)	8 (4.7)
Ethnicity		
Hispanic or Latino	16 (11.2)	51 (30.0)
Not Hispanic or Latino	126 (88.1)	119 (70.0)
Not reported	1 (0.7)	0

Note: Participants who had no serological or virological evidence (up to 1 month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at pre-Dose 1 and 1 month after Dose 2, SARS-CoV-2 not detected by NAAT [nasal swab] at pre-Dose 1 and pre-Dose 2, and negative NAAT [nasal swab] at any unscheduled visit up to 1 month after Dose 2 blood collection) and had no medical history of COVID-19 were included in the analysis.

a. N = Number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. Includes multiracial and not reported.

SARS-CoV-2 50% neutralizing antibody titers (NT50) were compared between an immunogenicity subset of Phase 2/3 participants 2 through 4 years of age from Study 3 at 1 month after the 3-dose primary course and a randomly selected subset from Study 2 (Phase 2/3) participants 16 through 25 years of age at 1 month after the 2-dose primary course, using a microneutralization assay against the reference strain (USA_WA1/2020). The primary

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immunobridging analyses compared the geometric mean titers (using a GMR) and the seroresponse (defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from before Dose 1) rates in the evaluable immunogenicity population of participants without evidence of prior SARS-CoV-2 infection up to 1 month after Dose 3 in participants 2 through 4 years of age and up to 1 month after Dose 2 in participants 16 through 25 years of age. The prespecified immunobridging criteria were met for both the GMR and the seroresponse difference (Table 22 and Table 23, respectively).

Table 22. SARS-CoV-2 GMTs (NT50) at 1 Month After Vaccination Course – Immunobridging Subset - Participants 2 Through 4 Years of Age (Study 3) 1 Month After Dose 3 and Participants 16 Through 25 Years of Age (Study 2) 1 Month After Dose 2 – Without Evidence of SARS-CoV-2 Infection – Evaluable Immunogenicity Population[102]

	TRADENAME		
	3 mcg/Dose 2 Through 4 Years of Age (1 month After Dose 3) n[a]=143	30 mcg/Dose 16 Through 25 Years of Age (1 Month After Dose 2) n[a]=170	GMR (95%CI) (2 Through 4 Years of Age/16 Through 25 Years of Age)[c,d]
Assay	GMT[b] (95% CI[b])	GMT[b] (95% CI[b])	
SARS-CoV-2 neutralization assay - NT50 (titer)[e]	1535.2 (1388.2, 1697.8)	1180.0 (1066.6, 1305.4)	1.30 (1.13, 1.50)

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Participants who had no serological or virological evidence [(up to 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3) blood sample collection)] of past SARS-CoV-2 infection [i.e., N-binding antibody [serum] negative at Dose 1, Dose 3 (Study 3) and 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3), SARS-CoV-2 not detected by NAAT [nasal swab] at Dose 1, Dose 2, and Dose 3 (Study 3) study visits, and negative NAAT [nasal swab] at any unscheduled visit up to 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3) blood collection] and had no medical history of COVID-19 were included in the analysis.

a. n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
b. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
c. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titers (2 to 4 years of age minus 16 to 25 years of age) and the corresponding CI (based on the Student t distribution).
d. Immunobridging is declared if the lower bound of the 2-sided 95% CI for the GMR ratio is greater than 0.67 and the point estimate of the GMR is ≥0.8.
e. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

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Table 23. Difference in Percentages of Participants With Seroresponse at 1 Month After Vaccination Course – Immunobridging Subset –Participants 2 Through 4 Years of Age (Study 3) 1 Month After Dose 3 and Participants 16 Through 25 Years of Age (Study 2) 1 Month After Dose 2 Without Evidence of Infection – Evaluable Immunogenicity Population[103]

	TRADENAME		
	3 mcg/Dose 2 Through 4 Years of Age (1 Month After Dose 3) N[a]=141	30 mcg/Dose 16 Through 25 Years of Age (1 Month After Dose 2) N[a]=170	Difference in Seroresponse Rates %[d] (95% CI[e]) (2 Through 4 Years of age Minus 16 Through 25 Years of Age)[f]
Assay	n[b] (%) (95% CI[c])	n[b] (%) (95% CI[c])	
SARS-CoV-2 neutralization assay - NT50 (titer)[g]	141 (100.0) (97.4, 100.0)	168 (98.8) (95.8, 99.9)	1.2 (-1.5, 4.2)

Abbreviations: LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer 50; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result ≥4 × LLOQ is considered a seroresponse.

Note: Participants who had no serological or virological evidence (up to 1 month after Dose 2 [(Study 2) or 1 month after Dose 3 (Study 3) blood sample collection)[of past SARS-CoV-2 infection [i.e., N-binding antibody [serum] negative at pre-Dose 1, pre-Dose 3 (Study 3) and 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3), SARS-CoV-2 not detected by NAAT [nasal swab] at pre-Dose 1, pre-Dose 2, and pre-Dose 3 (Study 3) study visits, and negative NAAT [nasal swab] at any unscheduled visit up to 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3) blood collection] and had no medical history of COVID-19 were included in the analysis.

a. N = Number of participants with valid and determinate assay results both before vaccination and at 1 month after Dose 2. These values are the denominators for the percentage calculations.
b. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.
c. Exact 2-sided CI based on the Clopper and Pearson method.
d. Difference in proportions, expressed as a percentage (2 through 4 years of age minus 16 through 25 years of age).
e. 2-sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
f. Immunobridging is declared if the lower bound of the 2-sided 95% CI for the difference in proportions is greater than -10.0% provided that the immunobridging criteria based on GMR were met.
g. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

Using a non-validated fluorescence focus reduction neutralization test assay against the Omicron variant of SARS-CoV-2 (BA.1), the NT50 GMT at 1 month after Dose 3 among a subset of 34 study participants without evidence of prior SARS-CoV-2 infection (82.5 [2-sided 95% CI: 55.4, 122.9]) was increased compared to the NT50 GMT before Dose 3 (14.0 [2-sided 95% CI: 10.6, 18.5]).

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An additional descriptive immunogenicity analysis was performed for participants 2 through 4 years of age who received a 3-dose course of TRADENAME in Study 3 (Phase 2/3), compared with a subset of participants 18 through 50 years of age in Study C4591017 (Phase 3) who had received a 2-dose primary course followed by a booster dose of TRADENAME 30 mcg. The comparator group (participants 18 through 50 years of age) in this analysis had a similar interval between TRADENAME Dose 2 and Dose 3 (median 13.0 weeks) as the participants 2 to 4 years of age (median 10.6 weeks). Among 34 participants 2 through 4 years of age without evidence of prior SARS-CoV-2 infection who received 3 doses of TRADENAME 3 mcg, neutralizing GMTs were 114.3 at 1-month post-Dose 3. Among 27 participants 18 through 50 years of age without evidence of prior SARS-CoV-2 infection who received 3 doses of TRADENAME 30 mcg, Omicron neutralizing GMTs were 164.2 at 1-month post-Dose 3.

Infants 6 through 23 months of age – after 3 doses[86]

A descriptive efficacy analysis of Study 3 has been performed in participants 6 through 23 months of age. This analysis evaluated confirmed symptomatic COVID-19 cases accrued up to a data cutoff date of 29 April 2022.

Table 24 presents the specific demographic characteristics in participants 6 through 23 months of age who received 3 doses of TRADENAME (3 mcg modRNA) or placebo.

Table 24. Demographics Characteristics – Phase 2/3 – Participants 6 Through 23 Months of Age – Dose 3 All-Available Efficacy Population[104]

	TRADENAME 3 mcg/Dose (N[a]=386) n[b] (%)	**Placebo (N[a]=184) n[b] (%)**
Sex		
Male	189 (49.0)	79 (42.9)
Female	197 (51.0)	105 (57.1)
Age at Vaccination (months)		
Mean (SD)	15.4 (4.92)	15.2 (5.14)
Median	16.0	15.5
Min, max	(6, 23)	(6, 23)
Race		
White	290 (75.1)	136 (73.9)
Black or African American	10 (2.6)	11 (6.0)
American Indian or Alaska Native	1 (0.3)	0
Asian	42 (10.9)	17 (9.2)
Other[c]	43 (11.1)	20 (10.9)
Ethnicity		
Hispanic or Latino	40 (10.4)	13 (7.1)
Not Hispanic or Latino	344 (89.1)	169 (91.8)
Not reported	2 (0.5)	2 (1.1)

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	TRADENAME 3 mcg/Dose (N[a]=386) n[b] (%)	Placebo (N[a]=184) n[b] (%)
Comorbidities[d]		
Yes	17 (4.4)	9 (4.9)
No	369 (95.6)	175 (95.1)

Abbreviation: SD = standard deviation.

a. N = Number of participants in the specified group from the Dose 3 all-available efficacy population. This value is the denominator for the percentage calculations. Dose 3 all-available efficacy population included all randomized participants who received 3 doses of TRADENAME (3 mcg modRNA) or placebo.
b. n = Number of participants with the specified characteristic.
c. Includes multiracial and not reported.
d. Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as participants who had at least 1 of the prespecified comorbidities based on Morbidity and Mortality Weekly Report 69(32);1081-1088.

The descriptive vaccine efficacy results after dose 3 in participants 6 through 23 months of age are presented in Table 25.

Table 25. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 3 – Phase 2/3 – Participants 6 Through 23 Months of Age – Dose 3 All-available Efficacy Population (Blinded Follow-up Period)[105]

	TRADENAME 3 mcg/Dose N[a]=386 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=184 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy (%) (95% CI[e])
First COVID-19 occurrence from 7 days after Dose 3	1 0.030 (277)	2 0.015 (139)	75.5 (-370.1, 99.6)

Abbreviation: VE = vaccine efficacy.

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; inability to eat/poor feeding).

a. N = Number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1,000 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 3 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Two-sided 95% confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.

Additional evaluation of vaccine efficacy for cases confirmed at least 7 days after Dose 2 and before Dose 3 was performed. In the evaluable efficacy population in participants without prior evidence of SARS-CoV-2 infection before or during the vaccination regimen the observed

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vaccine efficacy from at least 7 days after Dose 2 and before Dose 3 was 16.1% (2-sided 95% CI: -24.9%, 43.1%). The vaccine efficacy in participants with or without prior evidence of SARS-CoV-2 infection before or during the vaccination regimen was similar.

Analysis of COVID-19 cases that excluded those involving coinfection with other respiratory pathogens did not meaningfully impact the estimated vaccine efficacy in this population.

One participant in the placebo group, had confirmed COVID-19 which met a single severe case criterion described in the protocol (increased heart rate [172 bpm]). None of the cases accrued met criteria for multisystem inflammatory syndrome in children (MIS-C).

Immunogenicity analyses have been performed in the immunobridging subset of 82 Study 3 participants 6 through 23 months of age without evidence of infection up to 1 month after Dose 3 based on a data cutoff date of 29 April 2022.

Table 26 presents the specific demographic characteristics in the studied evaluable immunogenicity population.

Table 26. Demographics Characteristics – Immunobridging Subset – Participants 6 Through 23 Months of Age (Study 3) and Participants 16 Through 25 Years of Age (Study 2) – Without Evidence of Infection -Evaluable Immunogenicity Population[106]

	TRADENAME 3 mcg/Dose 6 Through 23 Months of Age (N[a]=82) n[b] (%)	**TRADENAME 30 mcg/Dose 16 Through 25 Years of Age (N[a]=170) n[b] (%)**
Sex		
Male	51 (62.2)	79 (46.5)
Female	31 (37.8)	91 (53.5)
Age at Vaccination (years)		
Mean (SD)	15.7 (4.84)	21.2 (2.95)
Median	16.0	2.0
Min, max	(6, 23)	(16, 25)
Race		
White	59 (72.0)	130 (76.5)
Black or African American	1 (1.2)	15 (8.8)
American Indian or Alaska Native	1 (1.2)	3 (1.8)
Asian	11 (13.4)	13 (7.6)
Native Hawaiian or other Pacific Islander	0	1 (0.6)
Other[c]	10 (12.2)	8 (4.7)

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	TRADENAME 3 mcg/Dose 6 Through 23 Months of Age (N[a]=82) n[b] (%)	TRADENAME 30 mcg/Dose 16 Through 25 Years of Age (N[a]=170) n[b] (%)
Ethnicity		
Hispanic or Latino	13 (15.9)	51 (30.0)
Not Hispanic or Latino	69 (84.1)	119 (70.0)

Note: Participants who had no serological or virological evidence (up to 1 month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at pre-Dose 1 and 1 month after Dose 2, SARS-CoV-2 not detected by NAAT [nasal swab] at pre-Dose 1 and pre-Dose 2, and negative NAAT [nasal swab] at any unscheduled visit up to 1 month after Dose 2 blood collection) and had no medical history of COVID-19 were included in the analysis.

a. N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. Includes multiracial and not reported.

SARS-CoV-2 50% neutralizing antibody titers (NT50) 1 month after the vaccination course were compared between an immunogenicity subset of Phase 2/3 participants 6 through 23 months of age from Study 3 and a randomly selected subset from Study 2 (Phase 2/3) participants 16 through 25 years of age, using a microneutralization assay against the reference strain (USA_WA1/2020). The primary immunobridging analyses compared the geometric mean titers (using a GMR) and the seroresponse (defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from before Dose 1) rates in the evaluable immunogenicity population of participants without evidence of prior SARS-CoV-2 infection up to 1 month after Dose 3 in participants 6 through 23 months of age and up to 1 month after Dose 2 in participants 16 through 25 years of age. The prespecified immunobridging criteria were met for both the GMR and the seroresponse difference (Table 27 and Table 28, respectively).

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Table 27. SARS-CoV-2 GMTs (NT50) at 1 Month After Vaccination Course – Immunobridging Subset - Participants 6 Through 23 Months of Age (Study 3) 1 Month After Dose 3 and Participants 16 rough 25 Years of Age (Study 2) 1 Month After Dose 2 – Without Evidence of SARS-CoV-2 – Evaluable Immunogenicity Population[107]

	TRADENAME		
	3 mcg/Dose 6 Through 23 Months of Age (1 Month After Dose 3) n^a=82	30 mcg/Dose 16 Through 25 Years of Age (1 Month After Dose 2) n^a=170	GMR (95%CI) (6 Through 23 Months of Age/16 Through 25 Years of Age)[c,d]
Assay	GMT[b] (95% CI[b])	GMT[b] (95% CI[b])	
SARS-CoV-2 neutralization assay - NT50 (titer)[e]	1406.5 (1211.3, 1633.1)	1180.0 (1066.6, 1305.4)	1.19 (1.00, 1.42)

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Participants who had no serological or virological evidence [(up to 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3) blood sample collection)] of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Dose 1, Dose 3 (Study 3) and 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3), SARS-CoV-2 not detected by NAAT [nasal swab] at Dose 1, Dose 2, and Dose 3 (Study 3) study visits, and negative NAAT [nasal swab] at any unscheduled visit up to 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3) blood collection)] and had no medical history of COVID-19 were included in the analysis.

a. n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
b. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
c. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titers (6 through 23 months of age minus 16 through 25 years of age) and the corresponding CI (based on the Student t distribution).
d. Immunobridging is declared if the lower bound of the 2-sided 95% CI for the GMR ratio is greater than 0.67 and the point estimate of the GMR is ≥0.8.
e. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

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Table 28. Difference in Percentages of Participants With Seroresponse at 1 Month After Vaccination Course – Immunobridging Subset – Participants 6 Through 23 Months of Age (Study 3) 1 Month After Dose 3 and Participants 16 Through 25 Years of Age (Study 2) to 1 Month After Dose 2 Without Evidence of Infection – Evaluable Immunogenicity Population[108]

	TRADENAME		
	3 mcg/Dose 6 Through 23 Months of Age (1 Month After Dose 3) N[a]=80	30 mcg/Dose 16 Through 25 Years of Age (1 Month After Dose 2) N[a]=170	Difference in Seroresponse Rates %[d] (95% CI[e]) (6 Through 23 Months of Age Minus 16 Through 25 Years of Age)[f]
Assay	n[b] (%) (95% CI[c])	n[b] (%) (95% CI[c])	
SARS-CoV-2 neutralization assay - NT50 (titer)[g]	80 (100.0) (95.5, 100.0)	168 (98.8) (95.8, 99.9)	1.2 (-3.4, 4.2,)

Abbreviations: LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer 50; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result ≥4 × LLOQ is considered a seroresponse.

Note: Participants who had no serological or virological evidence [(up to 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3) blood sample collection) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at pre-Dose 1, Dose 3 (Study 3) and 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3), SARS-CoV-2 not detected by NAAT [nasal swab] at pre-Dose 1, pre-Dose 2, and pre-Dose 3 (Study 3) study visits, and negative NAAT [nasal swab] at any unscheduled visit up to 1 month after Dose 2 (Study 2) or 1 month after Dose 3 (Study 3) blood collection)] and had no medical history of COVID-19 were included in the analysis.

a. N = Number of participants with valid and determinate assay results both before vaccination and at 1 month after Dose 2. These values are the denominators for the percentage calculations.
b. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.
c. Exact 2-sided CI based on the Clopper and Pearson method.
d. Difference in proportions, expressed as a percentage (6 through 23 months of age minus 16 through 25 years of age).
e. 2-sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
f. Immunobridging is declared if the lower bound of the 2-sided 95% CI for the difference in proportions is greater than -10.0% provided that the immunobridging criteria based on GMR were met.
g. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

Using a non-validated fluorescence focus reduction neutralization test assay against the Omicron variant of SARS-CoV-2 (BA.1), the NT50 GMT at 1 month after Dose 3 among a subset of 32 study participants without evidence of prior SARS-CoV-2 infection (127.5 [2-sided 95% CI: 90.2, 180.1]) was increased compared to the NT50 GMT before Dose 3 (16.3 [2-sided 95% CI: 12.8, 20.8]).

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An additional descriptive immunogenicity analysis was performed for participants 6 through 23 months of age who received a 3-dose course of TRADENAME in Study 3 (Phase 2/3), compared with a subset of participants 18 through 50 years of age in Phase 3 Study C4591017 who had received a 2-dose primary course followed by a booster dose of TRADENAME 30 mcg. The comparator group (participants 18 through 50 years of age) in this analysis had a similar interval between TRADENAME Dose 2 and Dose 3 (median 13.0 weeks) as the participants 6 through 23 months of age (median 12.9 weeks). Among 32 participants 6 through 23 months of age without evidence of prior SARS-CoV-2 infection who received 3 doses of TRADENAME 3 mcg, Omicron neutralizing GMTs were 128.8 at 1-month post-Dose 3. Among 27 participants 18 through 50 years of age without evidence of prior SARS-CoV-2 infection who received 3 doses of TRADENAME 30 mcg, Omicron neutralizing GMTs were 164.2 at 1-month post-Dose 3.

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

Effectiveness of a booster dose of TRADENAME was demonstrated by evaluating noninferiority immune responses of SARS-CoV-2 NT50 1 month after a booster dose. In Study 2, an analysis of SARS-CoV-2 NT50 demonstrated non-inferior immune responses 1 month after a booster dose compared to 1 month after Dose 2 in participants at least 18 through 55 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the booster dose, based on prespecified noninferiority criteria for both GMR and difference in seroresponse rates. Seroresponse for a participant was defined as achieving a ≥4-fold rise from baseline (before Dose 1) in NT50 (Table 29 and Table 30).

The SARS-CoV-2 NT50 GMR of 1 month after the booster dose to 1 month after Dose 2 was 3.26 (2-sided 97.5% CI: 2.76, 3.86), which met the noninferiority criteria for GMR (lower bound of the 2-sided 97.5% CI >0.67 and point estimate of the GMR ≥0.8).

A high proportion of participants (99.5%) had seroresponse 1 month after Dose 3 compared with 95.0% 1 month after Dose 2. The difference in proportions of participants with a seroresponse 1 month after the booster dose (Dose 3) and 1 month after Dose 2 (Dose 3 minus Dose 2) was 1.5% (2-sided 97.5% CI: 1.0%, 7.9%), which met the 10% noninferiority criterion (i.e., lower bound of the 2-sided 97.5% CI >10%).

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Table 29. Summary of Geometric Mean Ratio for 50% Neutralizing Titer – Comparison of 1 Month After Booster Dose to 1 Month After Dose 2 – Participants Without Evidence of Infection up to 1 Month After Booster Dose* – Booster Dose Evaluable Immunogenicity Population±,71,109,110

		TRADENAME Sampling Time Point			
		1 Month After Booster Dose	1 Month After Dose 2	1 Month After Booster Dose - 1 Month After Dose 2	Met Noninferiority Objective[d] (Y/N)
Assay	n[a]	GMT[b] (95% CI[b])	GMT[b] (95% CI[b])	GMR[c] (97.5% CI[c])	
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)[e]	212	2466.0 (2202.6, 2760.8)	755.7 (663.1, 861.2)	3.26 (2.76, 3.86)	Y

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

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

± All eligible participants who had received 2 doses of TRADENAME as initially randomized, with Dose 2 received within the predefined window (within 19 to 42 days after Dose 1), received a booster dose of TRADENAME, had at least 1 valid and determinate immunogenicity result after booster dose from a blood collection within an appropriate window (within 28 to 42 days after the booster dose), and had no other important protocol deviations as determined by the clinician.

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

b. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.

c. GMRs and 2-sided 97.5% CIs were calculated by exponentiating the mean differences in the logarithms of the assay and the corresponding CIs (based on the Student t distribution).

d. Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the GMR is >0.67 and the point estimate of the GMR is ≥0.80.

e. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

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Table 30. Percentage Difference of Participants Achieving Seroresponse – Comparison of 1 Month After Booster Dose to 1 Month After Dose 2 – Phase 3 – Participants Without Evidence of Infection up to 1 Month After Booster Dose* – Booster Dose Evaluable Immunogenicity Population±,71,110,111

		TRADENAME Sampling Time Point		Difference (1 Month After Booster Dose - 1 Month After Dose 2)	Met Noninferiority Objective[f] (Y/N)
		1 Month After Booster Dose	1 Month After Dose 2		
Assay	N[a]	n[b] % (95% CI[c])	n[b] % (95% CI[c])	%[d] (97.5% CI[e])	
SARS-CoV-2 neutralization assay - reference strain - NT50 (titer)[g]	200	199 99.5 (97.2, 100.0)	190 95.0 (91.0, 97.6)	4.5 (1.0, 7.9)	Y

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

Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result ≥4 × LLOQ is considered a seroresponse.

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

± All eligible participants who had received 2 doses of TRADENAME as initially randomized, with Dose 2 received within the predefined window (within 19 to 42 days after Dose 1), received a booster dose of TRADENAME, had at least 1 valid and determinate immunogenicity result after booster dose from a blood collection within an appropriate window (within 28 to 42 days after the booster dose), and had no other important protocol deviations as determined by the clinician.

a. N = number of participants with valid and determinate assay results for the specified assay at baseline, 1 month after Dose 2 and 1 month after the booster dose within specified window. These values are the denominators for the percentage calculations.

b. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.

c. Exact 2-sided CI based on the Clopper and Pearson method.

d. Difference in proportions, expressed as a percentage (1 month after booster dose – 1 month after Dose 2).

e. Adjusted Wald 2-sided CI for the difference in proportions, expressed as a percentage.

f. Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the percentage difference is >-10%.

g. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

Relative vaccine efficacy in participants 16 years of age and older – after booster dose[80,112,113]

An interim efficacy analysis of Study 4, a placebo-controlled booster study, was performed in approximately 10,000 participants 16 years of age and older who were recruited from Study 2, evaluated confirmed COVID-19 cases accrued from at least 7 days after booster vaccination up to a data cut-off date of 8 February 2022 (a period when Delta and then Omicron was the predominant variant), which represents a median of 2.8 months (range 0.3 to 7.5 months) post-booster follow-up. Vaccine efficacy of the TRADENAME booster dose after the primary series relative to the placebo booster group who only received the primary series dose was

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assessed. The relative vaccine efficacy information for participants 16 years of age and older is presented in Table 31.

Table 31. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Booster Vaccination – Participants 16 Years of Age and Older Without Evidence of Infection and Participants With or Without Evidence of Infection Prior to 7 Days After Booster Vaccination – Evaluable Efficacy Population[80,114,115]

First COVID-19 occurrence from 7 days after booster dose in participants without evidence of prior SARS-CoV-2 infection*			
	TRADENAME N[a]=4689 Cases n1[b] Surveillance Time[c] (n2[d])	**Placebo N[a]=4664 Cases n1[b] Surveillance Time[c] (n2[d])**	**Relative Vaccine Efficacy[e] % (95% CI[f])**
First COVID-19 occurrence from 7 days after booster vaccination	63 1.098 (4639)	148 0.932 (4601)	63.9 (51.1, 73.5)
First COVID-19 occurrence from 7 days after booster dose in participants with or without evidence of prior SARS-CoV-2 infection			
	TRADENAME N[a]=4997 Cases n1[b] Surveillance Time[c] (n2[d])	**Placebo N[a]=4942 Cases n1[b] Surveillance Time[c] (n2[d])**	**Relative Vaccine Efficacy[e] % (95% CI[f])**
First COVID-19 occurrence from 7 days after booster vaccination	67 1.179 (4903)	150 0.989 (4846)	62.4 (49.5, 72.2)

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 serological or virological evidence (prior to 7 days after receipt of the booster vaccination) 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 Visit 1, and had a negative NAAT [nasal swab] at any unscheduled visit prior to 7 days after booster vaccination) 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 the booster vaccination to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Relative vaccine efficacy of the TRADENAME booster group relative to the placebo group (non-booster).
f. Two-sided confidence interval (CI) for relative vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.

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Immunogenicity in children 5 through <12 years of age – after booster dose[84]

Effectiveness of a booster dose of TRADENAME was based on an assessment of NT50 against the reference strain of SARS-CoV-2 (USA_WA1/2020). Analyses of NT50 1 month after the booster dose compared to before the booster dose (Dose 3) demonstrated a substantial increase in GMTs in individuals 5 through <12 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the booster dose. This analysis is summarized in Table 32.

Table 32. Summary of Geometric Mean Titers – NT50 – Participants Without Evidence of Infection – Phase 2/3 – Immunogenicity Set – 5 Through <12 Years of Age – Evaluable Immunogenicity Population

		TRADENAME 10 mcg/Dose					
		3-Dose Set		2-Dose Set		Total	
Assay	Dose/ Sampling Time Point[a]	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])
SARS-CoV-2 neutralization assay - NT50 (titer)	1 month Prevax	79	20.5 (20.5, 20.5)	67	20.5 (20.5, 20.5)	146	20.5 (20.5, 20.5)
	1 month after Dose 2	29	1659.4 (1385.1, 1988.0)	67	1110.7 (965.3, 1278.1)	96	1253.9 (1116.0, 1408.9)
	3 months Prevax	67	271.0 (229.1, 320.6)	-	-	67	271.0 (229.1, 320.6)
	1 month after Dose 3	67	2720.9 (2280.1, 3247.0)	-	-	67	2720.9 (2280.1, 3247.0)

Abbreviations: CI = confidence interval; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer; Prevax = before vaccination; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Three-dose immunogenicity set included the first 130 participants who received Dose 3 and completed 1-month post–Dose 3 visit prior to March 15, 2022. Among those, 30 had blood sample collection at 1-month post-Dose 2. Two-dose immunogenicity set included an extra 67 participants randomly selected from previous Dose-2 evaluable immunogenicity population and without evidence of infection up to 1-month post–Dose 2 subset used for 2-dose immunobridging analysis.
Note: Participants included in this analysis had no serological or virological evidence of past SARS-CoV-2 infection up to the 1-month post–Dose 2 (for 1-month post–Dose 2 time point) or 1-month post–Dose 3 (for pre–Dose 3 and 1-month post–Dose 3 time point) study blood sample collection. Having no evidence of past SARS-CoV-2 infection up to 1-month post–Dose 2 was defined as having a negative N-binding antibody (serum) result at the Dose 1 and 1-month post–Dose 2 study visits; a negative NAAT (nasal swab) result at the Dose 1 and Dose 2 study visits and any unscheduled visit prior to the 1-month post–Dose 2 blood sample collection; and no medical history of COVID-19. Having no evidence of past SARS-CoV-2 infection up to 1-month post-Dose 3 was defined as having a negative N-binding antibody (serum) result at the Dose 1, 1-month post–Dose 2 (if available), Dose 3, and 1-month post–Dose 3 study visits; a negative NAAT (nasal swab) result at the Dose 1, Dose 2, and Dose 3 study visits and any unscheduled visit prior to the 1-month post–Dose 3 blood sample collection; and no medical history of COVID-19.
a. Protocol-specified timing for blood sample collection.
b. n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.

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c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.

Immunogenicity in children 5 through <12 years of age on the Omicron variant – after booster dose[84]

The neutralizing GMTs against both the Omicron variant and reference strain were substantially increased after booster vaccination compared with after the 2-dose primary series. At 1-month post-Dose 2, the observed neutralizing GMTs for the Omicron variant and reference strain were 27.6 and 323.8, respectively. At 1-month post-Dose 3, the observed neutralizing GMTs for the Omicron variant and reference strain were 614.4 and 1702.8, respectively (see Table 33).

For the Omicron variant, neutralizing titers after booster vaccination (1-month post-Dose 3) increased 22-fold over those after the 2-dose primary series (1-month post-Dose 2). For the reference strain, the increase after the booster relative to the primary series was 5.3-fold.

Table 33. Summary of Geometric Mean Titers – Omicron-Neutralization Subset – Participants Without Evidence of Infection – Phase 2/3 – Immunogenicity Set – 5 Through <12 Years of Age – Evaluable Immunogenicity Population

		TRADENAME 10 mcg/Dose	
		Vaccine Group (as Randomized)	
Assay	Time Point[b]	n[b]	GMT[c] (95% CI[c])
SARS-COV-2 FFRNT- B.1.1.529 strain (Omicron) - NT50 (titer)	1 month after Dose 2	29	27.6 (22.1, 34.5)
	1 month after Dose 3	17	614.4 (410.7, 919.2)
SARS-CoV-2 FFRNT- reference strain - NT50 (titer)	1 month after Dose 2	29	323.8 (267.5, 392.1)
	1 month after Dose 3	17	1702.8 (1282.6, 2260.7)

Abbreviations: CI = confidence interval; FFRNT = fluorescence focus reduction neutralization test; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Participants included in this analysis had no serological or virological evidence of past SARS-CoV-2 infection up to the 1-month post–Dose 2 (for 1-month post–Dose 2 time point) or 1-month post–Dose 3 (for 1-month post–Dose 3 time point) study blood sample collection. Having no evidence of past SARS-CoV-2 infection up to 1-month post–Dose 2 was defined as having a negative N-binding antibody (serum) result at the Dose 1 and 1-month post–Dose 2 study visits; a negative NAAT (nasal swab) result at the Dose 1 and Dose 2 study visits and any unscheduled visit prior to the 1-month post–Dose 2 blood sample collection; and no medical history of COVID-19. Having no evidence of past SARS-CoV-2 infection up to 1-month post–Dose 3 was defined as having a negative N-binding antibody (serum) result at the Dose 1, 1-month post–Dose 2 (if available), Dose 3, and 1-month post–Dose 3 study visits; a negative NAAT (nasal swab) result at the Dose 1, Dose 2, and Dose 3 study visits and any unscheduled visit prior to the 1-month post–Dose 3 blood sample collection; and no medical history of COVID-19.

a. Protocol-specified timing for blood sample collection.

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b. n = Number of participants with valid and determinate assay results for the specified assays at the given dose/sampling time point.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.

Omicron-adapted TRADENAME

The efficacy of a booster dose of TRADENAME (Bivalent) is inferred from clinical data from the studies of a booster dose of an Omicron BA.1 adapted vaccine.

Immunogenicity in participants greater than 55 years of age – after a booster dose of TRADENAME (Bivalent, Original/Omicron BA.1) (fourth dose)

In an analysis of a subset from Study 4 (Substudy E), 610 adults greater than 55 years of age who had completed a series of 3 doses of TRADENAME received 1 of the following as a booster dose (fourth dose): TRADENAME (30 mcg) or TRADENAME (Bivalent, Original/Omicron BA.1) 15/15 mcg.[140] GMRs and seroresponse rates were evaluated at 1 month after TRADENAME (Bivalent, Original/Omicron BA.1)15/15 mcg booster vaccination.[141] TRADENAME (Bivalent, Original/Omicron BA.1) 15/15 mcg booster dose was administered 4.7 to 11.5 months (median 6.3 months) after the third dose.[140]

The primary objective of the analysis was to assess superiority with respect to level of neutralizing titer and noninferiority with respect to seroresponse rate of the anti-Omicron immune response induced by a dose of TRADENAME (Bivalent, Original/Omicron BA.1) 15/15 mcg relative to the response elicited by a dose of TRADENAME (30 mcg) given as a fourth dose in TRADENAME-experienced participants greater than 55 years of age.

Superiority of TRADENAME (Bivalent, Original/Omicron BA.1) 15/15 mcg to TRADENAME (30 mcg) was met, as the lower bound of the 2-sided 95% CI for GMR was >1 (Table 34).[142]

The difference in proportions of participants who achieved seroresponse between the Omicron BA.1 (15/15 mcg) group and TRADENAME (30 mcg) group was 14.6 (2-sided 95% CI: 4.0, 24.9). Noninferiority was met, as the lower limit of the 2-sided 95% CI for the difference in percentages of participants with seroresponse was >-5% (Table 35).[143,154]

Table 34: Substudy E - Geometric Mean Ratios for Between Vaccine Group Comparison – Participants Without Evidence of Infection Up to 1 Month after Dose 4 – Expanded Cohort – Immunogenicity Subset – Participants Greater Than 55 Years of Age – Evaluable Immunogenicity Population[144]

Assay	Vaccine Group (as randomized)	Sampling Time Point[a]	N[b]	GMT (95% CI[c])	GMR (95% CI[d])
SARS-CoV-2 neutralization assay - Omicron BA.1 - NT50 (titer)	TRADENAME (30 mcg)	1 month	163	455.8 (365.9, 567.6)	
	TRADENAME(Bivalent) BA.1 (15/15 mcg)	1 month	178	711.0 (588.3, 859.2)	1.56 (1.17, 2.08)

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Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Immunogenicity subset = a random sample of 230 participants in each vaccine group selected from the expanded cohort.
Note: Participants who had no serological or virological evidence (prior to the 1-month post–study vaccination blood sample collection) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] result negative at the study vaccination and the 1-month post–study vaccination visits, negative NAAT [nasal swab] result at the study vaccination visit, and any unscheduled visit prior to the 1-month post–study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.
a. Protocol-specified timing for blood sample collection.
b. n = number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
d. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titers (vaccine group in the corresponding row - Comirnaty [30 mcg]) and the corresponding CI (based on the Student t distribution).

Table 35: Substudy E - Number (%) of Participants Achieving Seroresponse – Participants Without Evidence of Infection Up to 1 Month after Dose 4 – Expanded Cohort – Immunogenicity Subset – Participants Greater Than 55 Years of Age – Evaluable Immunogenicity Population[145]

Assay	Vaccine Group (as randomized)	Sampling Time Point[a]	N[b]	n[c] (%) (95% CI[d])	Difference %[e] (95% CI[f])
SARS-CoV-2 neutralization assay - Omicron BA.1 - NT50 (titer)	TRADENAME (30 mcg)	1 month	149	85 (57.0) (48.7, 65.1)	
	TRADENAME (Bivalent BA.1) (15/15 mcg)	1 month	169	121 (71.6) (64.2, 78.3)	14.6 (4.0, 24.9)

Abbreviations: LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Immunogenicity subset = a random sample of 230 participants in each vaccine group selected from the expanded cohort.
Note: Seroresponse is defined as achieving ≥4-fold rise from baseline (before the study vaccination). If the baseline measurement is below the LLOQ, the postvaccination measure of ≥4 × LLOQ is considered a seroresponse.
Note: Participants who had no serological or virological evidence (prior to the 1-month post–study vaccination blood sample collection) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] result negative at the study vaccination and the 1-month post–study vaccination visits, negative NAAT [nasal swab] result at the study vaccination visit, and any unscheduled visit prior to the 1-month post–study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.
a. Protocol-specified timing for blood sample collection.
b. N = Number of participants with valid and determinate assay results for the specified assay at both the pre-vaccination time point and the given sampling time point. This value is the denominator for the percentage calculation.
c. n = Number of participants with seroresponse at 1 month after vaccination for the given assay.
d. Exact 2-sided CI based on the Clopper and Pearson method.
e. Difference in proportions, expressed as a percentage (vaccine group in the corresponding row - Comirnaty [30 mcg]).
f. Two-sided CI based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.

Immunogenicity in participants 18 to ≤55 years of age – after a booster dose of TRADENAME or monovalent Omicron BA.1 (fourth dose)

In Substudy D [a subset from Study 2 (Phase 3) and Study 4 (Phase 3)], 640 participants 18 to ≤55 years of age who had completed 3 doses of TRADENAME received 1 of the following as a booster (fourth dose):[146,147] TRADENAME (30 mcg) or monovalent Omicron BA.1 90 to 180 days after receiving Dose 3.[147]

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In the primary immunogenicity subset of participants without prior evidence of infection up to 1 month after Dose 4, the ratio of GMTs for the monovalent Omicron BA.1 group to the TRADENAME group GMR was 1.75 (2-sided 95% CI: 1.39, 2.22) (Table 36).[148]

The lower bound of the 2-sided 95% CI for GMR was >1, which meets the prespecified simple superiority criterion. Therefore, superiority of monovalent Omicron BA.1 to TRADENAME for the Omicron variant was achieved based on the GMR at 1 month after Dose 4.[148]

The difference in proportions of participants who achieved seroresponse between the monovalent Omicron BA.1 group and TRADENAME group was 23.0% (2-sided 95% CI: 11.1, 34.3)[149] (Table 37), the noninferiority criterion (lower bound of the 2-sided 95% CI >-5)[150] was achieved.

Table 36: Substudy D – Geometric Mean Ratios for Between Vaccine Group Comparison - Cohort 2 - Primary Immunogenicity Subset - Participants Without Evidence of Infection Up to 1 Month After Dose 4 - Evaluable Immunogenicity Population[151]

		Vaccine Group (as randomized)				
		Monovalent Omicron BA.1 (30 mcg)		TRADENAME (30 mcg)		Monovalent Omicron BA.1 / TRADENAME
Assay	Dose/ Sampling Time Point[a]	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])	GMR[d] (95% CI)[d]
SARS-CoV-2 neutralization assay - Omicron BA.1 - NT50 (titer)	1/1 month	132	1929.2 (1631.5, 2281.1)	141	1099.6 (932.0, 1297.4)	1.75 (1.39, 2.22)

Abbreviations: GMT = geometric mean titer; GMR = geometric mean ratio; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Primary immunogenicity subset = a random sample of 175 participants in each vaccine group selected from the full expanded set.

Note: Participants who had no serological or virological evidence (prior to the 1-month post–first study vaccination blood sample collection) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at the first study vaccination and the 1-month post–first study vaccination visits, negative NAAT [nasal swab] at the first study vaccination visit, and any unscheduled visit prior to the 1-month post–first study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.

a. Protocol-specified timing for blood sample collection.
b. n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
d. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titers (monovalent Omicron BA.1 [30 mcg] - Comirnaty [30 mcg]) and the corresponding CI (based on the Student t distribution).

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Table 37: Substudy D – Difference in Percentages of Participants With Seroresponse - Cohort 2 – Primary Immunogenicity Subset - Participants Without Evidence of Infection Up to 1 Month After Dose 4 - Evaluable Immunogenicity Population[149]

		Vaccine Group (as randomized)				
		Monovalent Omicron BA.1 (30 mcg)		TRADENAME (30 mcg)		Difference
Assay	Dose/Sampling Time Point[a]	N[a]	n[b] (%) (95% CI[c])	N[a]	n[b] (%) (95% CI[c])	% [d] (95% CI[e])
SARS-CoV-2 neutralization assay - Omicron BA.1 - NT50 (titre)	1/1 month	130	81 (62.3) (53.4, 70.7)	140	55 (39.3) (31.1, 47.9)	23.0 (11.1, 34.3)

Abbreviations: LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Seroresponse is defined as achieving a ≥ 4-fold rise from baseline (before the first dose of study vaccination). If the baseline measurement is below the LLOQ, the postvaccination measure of ≥4 × LLOQ is considered seroresponse.
Note: Primary immunogenicity subset = a random sample of 175 participants in each vaccine group selected from the full expanded set.
Note: Participants who had no serological or virological evidence (prior to the 1-month post–first study vaccination blood sample collection) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at the first study vaccination and the 1-month post–first study vaccination visits, negative NAAT [nasal swab] at the first study vaccination visit, and any unscheduled visit prior to the 1-month post–first study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.
a. N = number of participants with valid and determinate assay results for the specified assay at both the pre-vaccination time point and the given sampling time point. This value is the denominator for the percentage calculations.
b. n = Number of participants with seroresponse for the given assay at the given sampling time point.
c. Exact 2-sided CI based on the Clopper and Pearson method.
d. Difference in proportions, expressed as a percentage (monovalent Omicron BA.1 [30 mcg] - Comirnaty [30 mcg]).
e. 2-sided CI based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.

5.2. Pharmacokinetic properties

Not applicable.

5.3. Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients[2,3,74,116]

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

TRADENAME (Dilute Before Use)
(4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)
2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC0159)

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1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
Cholesterol
Potassium chloride
Potassium dihydrogen phosphate
Sodium chloride
Disodium hydrogen phosphate dihydrate
Sucrose
Water for injections

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

TRADENAME (Do Not Dilute)

Or

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

TRADENAME (for age 5 years to <12 years)

Or

*[Editorial Guidance for countries: Select this text for the **Tris/Sucrose presentation, 3 micrograms/dose.**]*

TRADENAME (for age 6 months to <5 years)

Or

*[Editorial guidance for countries: Select this text for the **Bivalent (Original/Omicron) presentation, 15/15 micrograms/dose**.]*

TRADENAME (Bivalent)

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

6.2. Incompatibilities

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

6.3. Shelf life

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

TRADENAME (Dilute Before Use)

Unopened vial

12 months at -90 °C to -60 °C.[63,70,83]

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 ºC to -60 ºC; not exceeding the printed expiry date (EXP).[39]

Once removed from the freezer, the unopened vial can be stored for up to 1 month at 2 °C to 8 °C; not exceeding the printed expiry date (EXP). Within the 1-month shelf life at 2 °C to 8 °C, up to 48 hours may be used for transportation.[29,63,117] 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

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

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

TRADENAME (Do Not Dilute)[75]

Or

*[Editorial guidance for countries: Select this text for the **Bivalent (Original/Omicron) presentation, 15/15 micrograms/dose**.]*

TRADENAME (Bivalent)

Unopened vial

12 months when stored at -90 °C to -60 °C.[79,83]

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

Once removed from frozen storage, the unopened vial may be stored refrigerated at 2 °C to 8 °C for a single period of up to 10 weeks; not exceeding the printed expiry date (EXP).[79]

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

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

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

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

Thawed vials can be handled in room light conditions.

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

Opened vial

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Chemical and physical in-use stability has been demonstrated for 12 hours at 2 ºC to 30 ºC. From a microbiological point of view, unless the method of opening precludes the risks of microbial contamination, the product should be used immediately after the first puncture. If not used immediately, in-use storage times and conditions are the responsibility of the user.[77]

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

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

Unopened vial

12 months when stored at -90 °C to -60 °C.[79,83]

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

Once removed from frozen storage, the unopened vial may be stored refrigerated at 2 °C to 8 °C for a single period of up to 10 weeks; not exceeding the printed expiry date (EXP).[79]

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

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

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

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

Thawed vials can be handled in room light conditions.

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

Diluted medicinal product

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

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*[Editorial Guidance for countries: Select this text for the **Tris/Sucrose presentation, 3 micrograms/dose**.]*

TRADENAME (for age 6 months to <5 years)[118]

Unopened vial

12 months when stored at -90 °C to -60 °C.

TRADENAME (for age 6 months to <5 years) will be received frozen at -90 °C to -60 °C.[76] Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

Once removed from frozen storage, the unopened vial may be stored refrigerated at 2 °C to 8 °C for a single period of up to 10 weeks; not exceeding the printed expiry date (EXP).

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

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

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

Vaccine may be stored at temperatures between 8 ºC to 30 ºC for up to 24 hours, including any time at these temperatures following dilution.

Thawed vials can be handled in room light conditions.

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

Diluted medicinal product[119]

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

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6.4. Special precautions for storage[2,25,75,101]

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

TRADENAME (Dilute Before Use)

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

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

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

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

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

TRADENAME (Do Not Dilute)

Or

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

TRADENAME (for age 5 years to <12 years)

Or

*[Editorial Guidance for countries: Select this text for the **Tris/Sucrose presentation, 3 micrograms/dose.]***

TRADENAME (for age 6 months to <5 years)

Or

*[Editorial guidance for countries: Select this text for the **Bivalent (Original/Omicron) presentation, 15/15 micrograms/dose**.]*

TRADENAME (Bivalent)

TRADENAME (Do Not Dilute),TRADENAME (for age 5 years to <12 years), TRADENAME (for age 6 months to <5 years), and {{TRADENAME (Bivalent)}} can be stored in a refrigerator at 2 °C to 8 °C for a single period of up to 10 weeks, not exceeding the original expiry date

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(EXP). Alternatively, the vaccine may be stored in a freezer at -90 °C to -60 °C. The expiry date for storage at -90 °C to -60 °C is printed on the vial and outer carton after "EXP".

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

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

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

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

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

Once thawed, the vaccine cannot be re-frozen.

Thawed vials can be handled in room light conditions.

6.5. Nature and contents of container

Information to be provided by local subsidiary.

6.6. Special precautions for disposal and other handling[2,3,26,29,30,35,63,75,77,78,116,117,118,119,152,153]

Handling instructions

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

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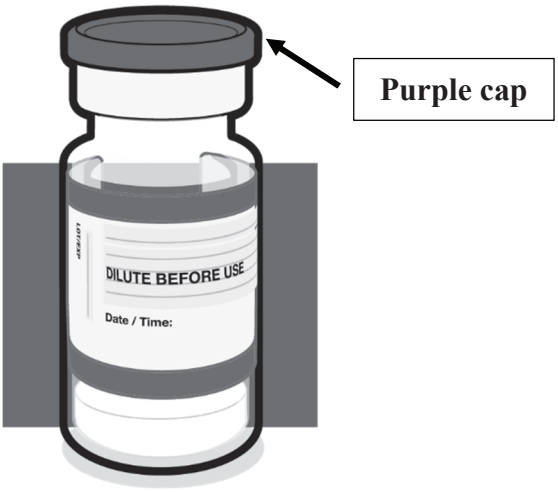
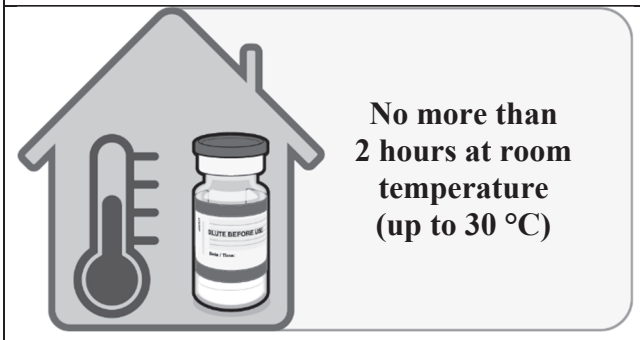
*[Editorial guidance for countries: Select this text for the **PBS/Sucrose presentation, 30 micrograms/dose**.]*

TRADENAME (Dilute Before Use)	
VIAL VERIFICATION	
	Verify that the vial has a purple plastic cap. If the vial has a grey plastic cap, refer to the handling instructions for TRADENAME (Do Not Dilute). If the vial has an orange plastic cap, refer to the handling instructions for TRADENAME (for ages 5 years to <12 years). If the vial has a maroon plastic cap, refer to the handling instructions for TRADENAME (for age 6 months to <5 years).
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; not exceeding the printed expiry date (EXP). Within the 1-month shelf life at 2 °C to 8 °C, up to 48 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.

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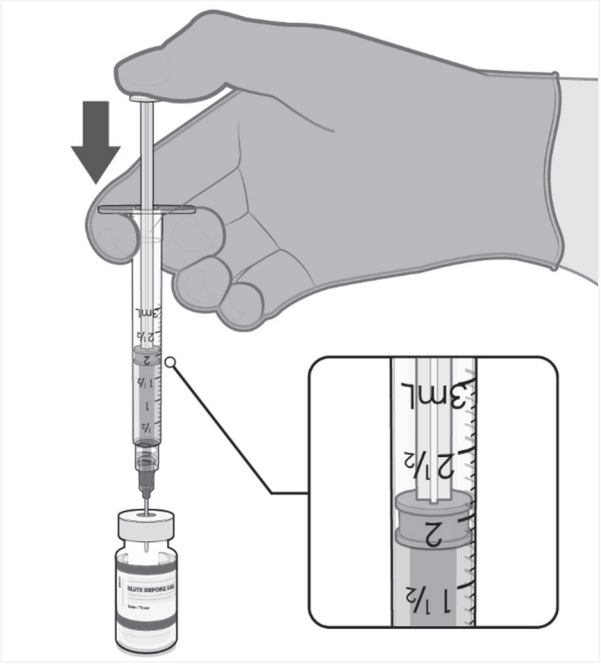
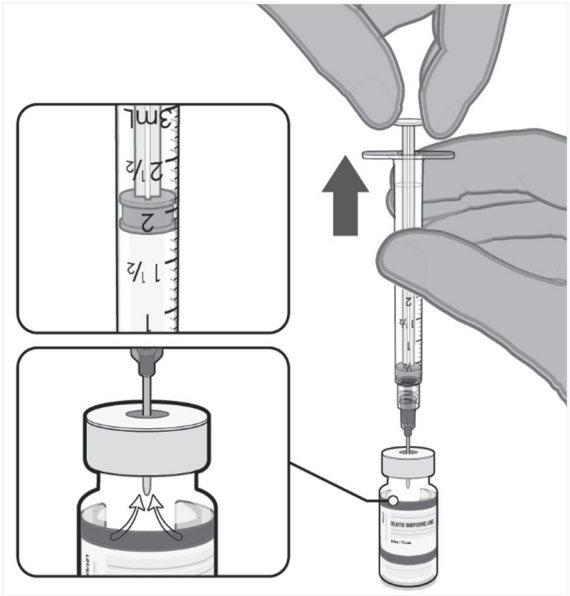
TRADENAME (Dilute Before Use)	
DILUTION	
 **1.8 mL of 0.9% sodium chloride injection**	• The thawed vaccine must be diluted in its original vial with 1.8 mL sodium chloride 9 mg/mL (0.9%) solution for injection, using a 21 gauge or narrower needle and aseptic techniques.
 **Pull back plunger to 1.8 mL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

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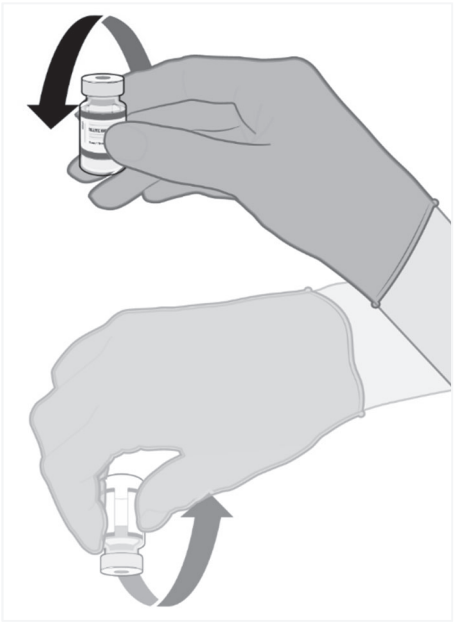
TRADENAME (Dilute Before Use)	
 **Gently × 10**	• Gently invert the diluted dispersion 10 times. Do not shake. • The diluted vaccine should present as an off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discoloration are present.
 **Record appropriate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

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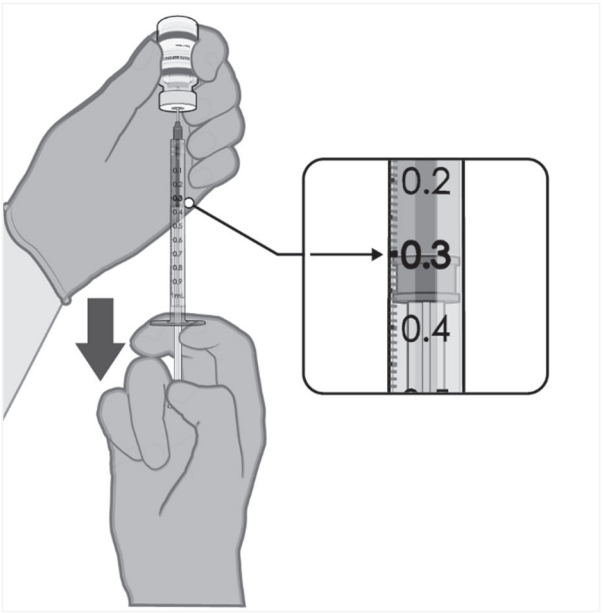
TRADENAME (Dilute Before Use)	
PREPARATION OF INDIVIDUAL 0.3 mL DOSES OF TRADENAME	
 **0.3 mL diluted vaccine**	• After dilution, the vial contains 2.25 mL from which 6 doses of 0.3 mL can be extracted. • Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab. • Withdraw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

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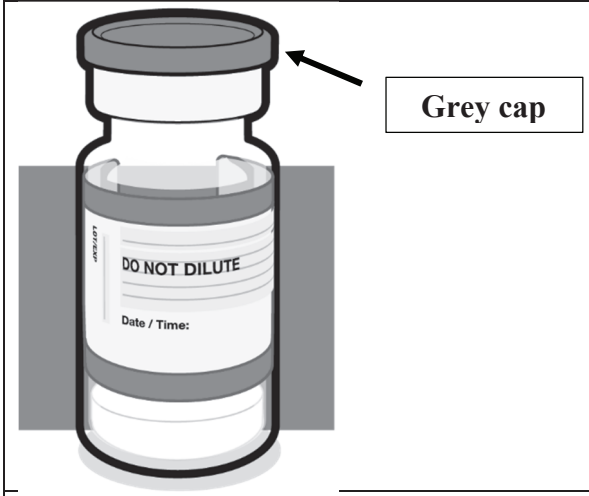
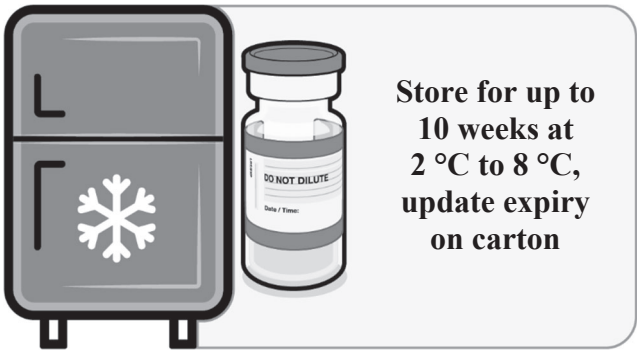
*[Editorial guidance for countries: Select this text for the **Tris/Sucrose presentation, 30 micrograms/dose**.]*

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

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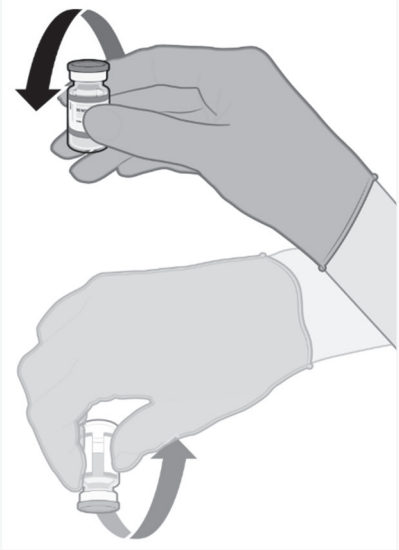
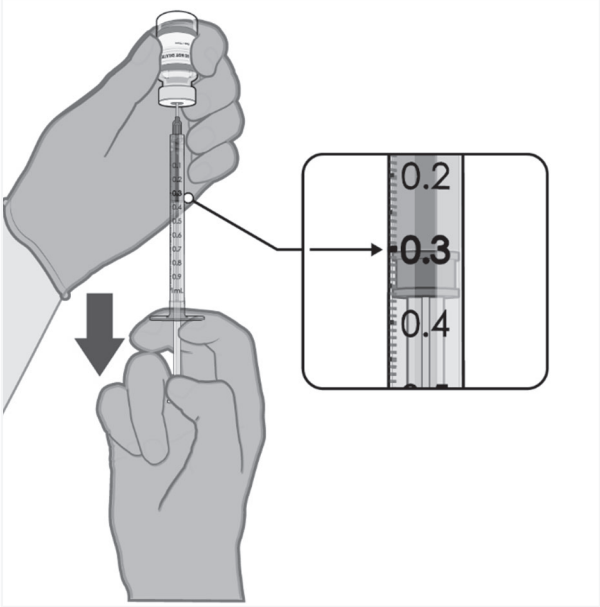
TRADENAME (Do Not Dilute)	
 **Gently × 10**	• Gently mix by inverting vials 10 times prior to use. Do not shake. • Prior to mixing, the thawed dispersion may contain white to off-white opaque amorphous particles. • After mixing, the vaccine should present as a white to off-white dispersion with no particulates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

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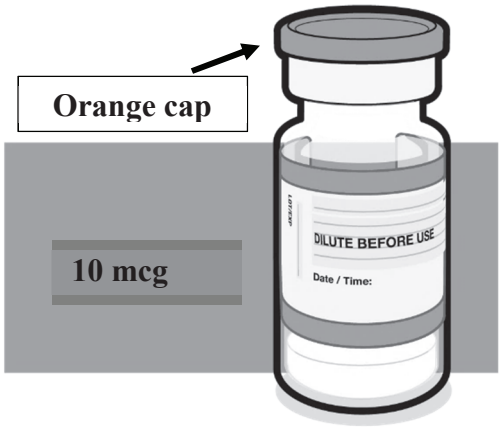
*[Editorial guidance for countries: Select this text for the **Tris/Sucrose presentation, 10 micrograms/dose**.]*

TRADENAME (for age 5 years to <12 years)	
VIAL VERIFICATION	
	• Verify that the vial has an orange plastic cap. If the vial has a purple plastic cap, refer to the handling instructions for TRADENAME (Dilute Before Use). If the vial has a grey plastic cap, refer to the handling instructions for TRADENAME (Do Not Dilute). If the vial has a maroon plastic cap, refer to the handling instructions for TRADENAME (for age 6 months to <5 years).
HANDLING PRIOR TO USE	
	• If the multidose vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 10 vial pack may take 4 hours to thaw. Ensure vials are completely thawed prior to use. • Unopened vials can be stored for up to 10 weeks at 2 °C to 8 °C; not exceeding the printed expiry date (EXP). • Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C for immediate use.

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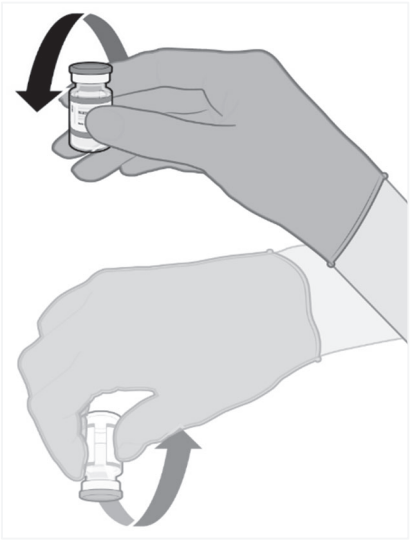
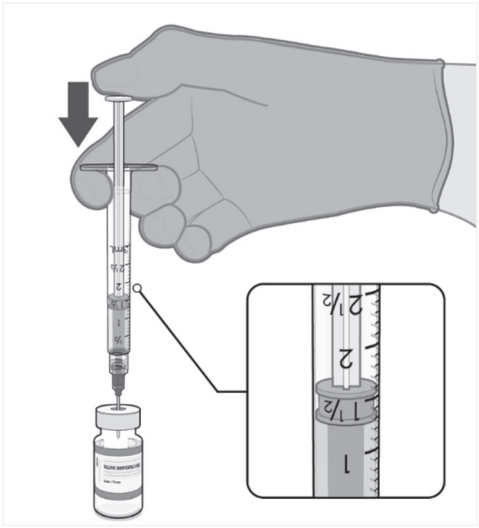
TRADENAME (for age 5 years to <12 years)	
MIXING PRIOR TO DILUTION	
 **Gently × 10**	• Allow the thawed vial to come to room temperature and gently invert it 10 times prior to dilution. Do not shake. • Prior to dilution, the thawed dispersion may contain white to off-white opaque amorphous particles.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

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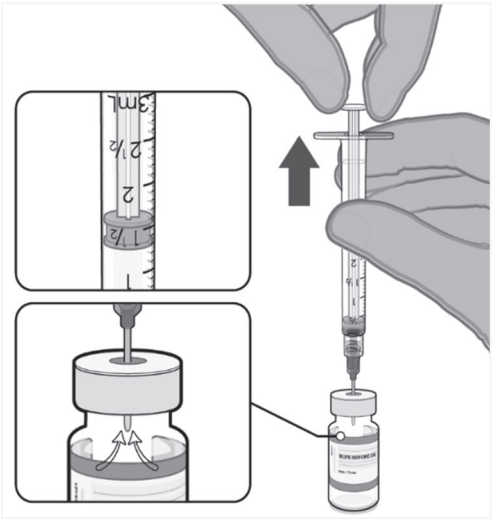
TRADENAME (for age 5 years to <12 years)	
 **Pull back plunger to 1.3 mL to remove air from vial.**	• Equalize vial pressure before removing the needle from the vial stopper by withdrawing 1.3 mL air into the empty diluent syringe.
 **Gently × 10**	• Gently invert the diluted dispersion 10 times. Do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

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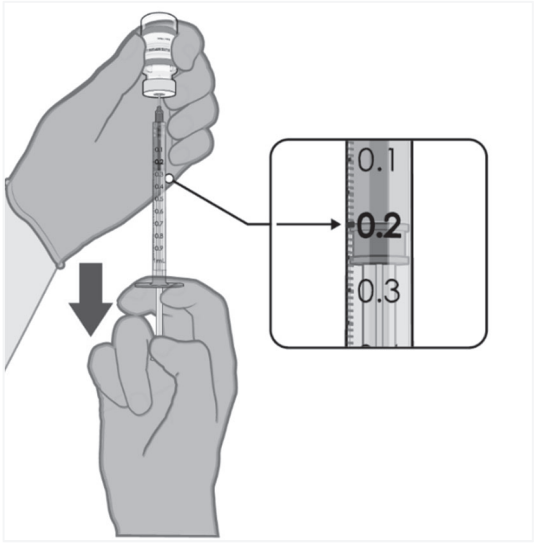
TRADENAME (for age 5 years to <12 years)	
 **Record appropriate date and time.** **Use within 12 hours after dilution.**	• The diluted vials should be marked with the appropriate date and time. • After dilution, store at 2 ºC to 30 ºC and use within 12 hours. • Do not freeze or shake the diluted dispersion.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

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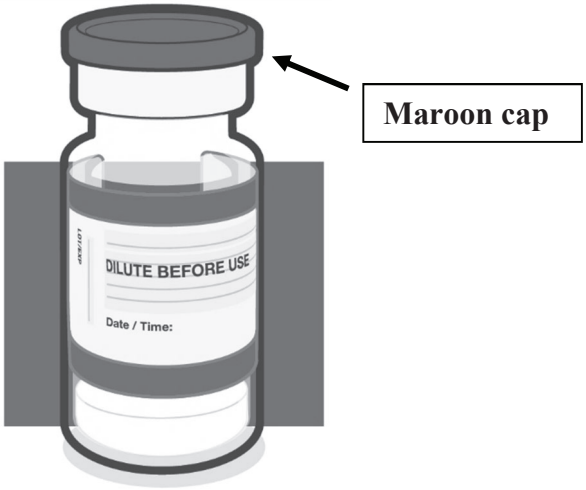
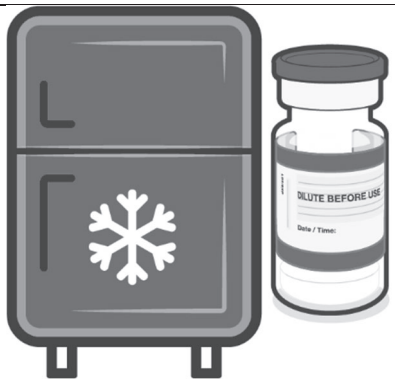
*[Editorial guidance for countries: Select this text for the **Tris/Sucrose presentation, 3 micrograms/dose**.]*

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

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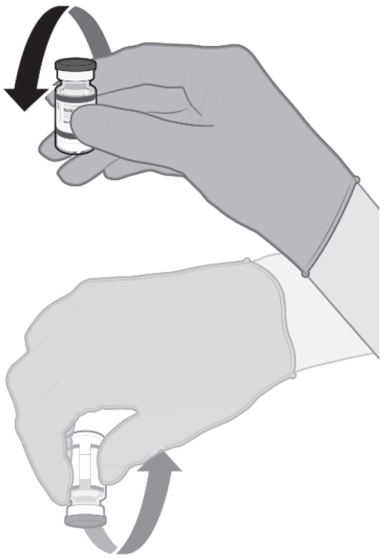
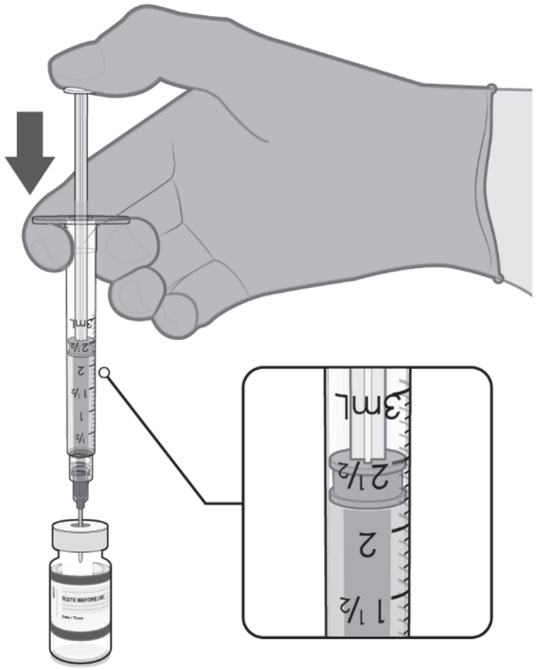
TRADENAME (for age 6 months to <5 years)	
MIXING PRIOR TO DILUTION	
 **Gently × 10**	• Allow the thawed vial to come to room temperature and gently invert it 10 times prior to dilution. Do not shake. • Prior to dilution, the thawed dispersion may contain white to off-white opaque amorphous particles.
DILUTION	
 **2.2 mL of 0.9% sodium chloride**	• The thawed vaccine must be diluted in its original vial with 2.2 mL sodium chloride 9 mg/mL (0.9%) solution for injection, using a 21 gauge or narrower needle and aseptic techniques.

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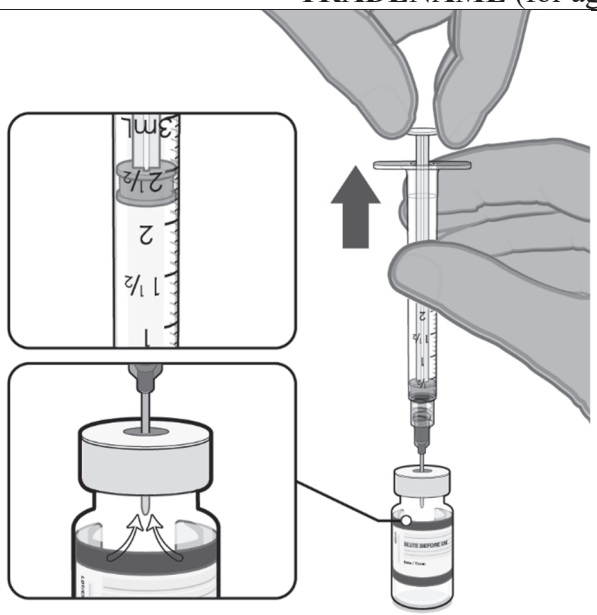
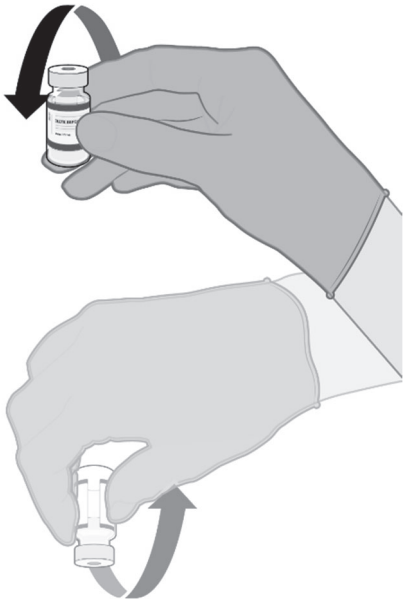
TRADENAME (for age 6 months to <5 years)	
 **Pull back plunger to 2.2 mL to remove air from vial.**	• Equalize vial pressure before removing the needle from the vial stopper by withdrawing 2.2 mL air into the empty diluent syringe.
 **Gently × 10**	• Gently invert the diluted dispersion 10 times. Do not shake. • The diluted vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discoloration are present.

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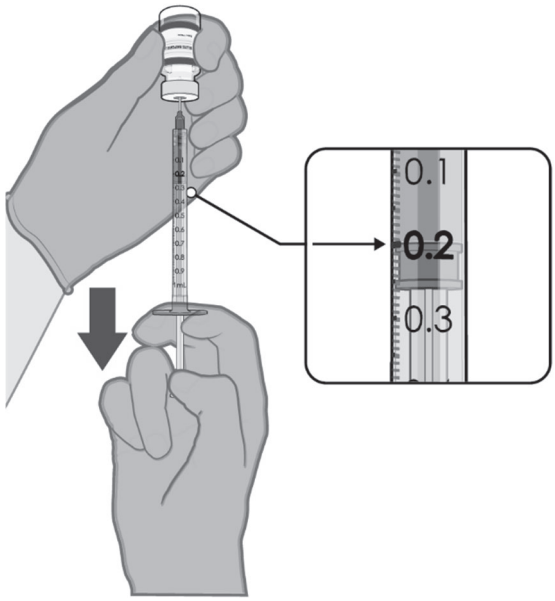
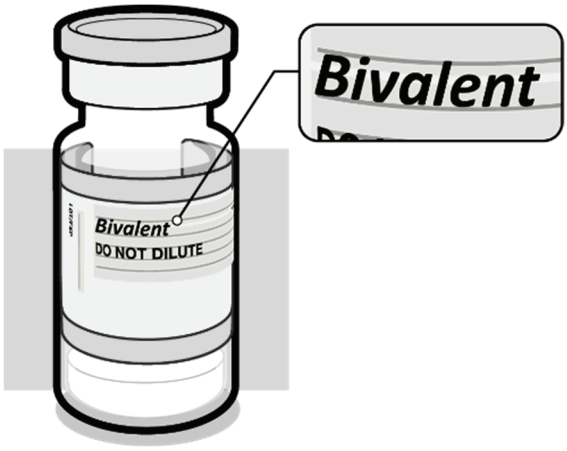
TRADENAME (for age 6 months to <5 years)	
 **Record appropriate date and time.** **Use within 12 hours after dilution.**	• The diluted vials should be marked with the appropriate date and time. • After dilution, store at 2 ºC to 30 ºC and use within 12 hours. • Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.
PREPARATION OF INDIVIDUAL 0.2 mL DOSES OF TRADENAME	
 **0.2 mL diluted vaccine**	• Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab. • Withdraw 0.2 mL of TRADENAME for individuals 6 months through <5 years of age. Low dead-volume syringes and/or needles should be used in order to extract 10 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microliters. If standard syringes and needles are used, there may not be sufficient volume to extract ten doses from a single vial. • Each dose must contain 0.2 mL of vaccine. • If the amount of vaccine remaining in the vial cannot provide a full dose of 0.2 mL, discard the vial and any excess volume. • Discard any unused vaccine within 12 hours after dilution.

*[Editorial guidance for countries: Select this text for the **Bivalent (Original/Omicron) presentation, 15/15 micrograms/dose**]*

TRADENAME (Bivalent)	
VIAL VERIFICATION	
 ✓ **Gray cap and label with gray border.**	• Verify that the vial has a grey cap and a grey border around the label and the product name is TRADENAME (Bivalent) 15/15 micrograms per dose dispersion for injection. • If the vial has a grey plastic cap and a grey border and the product name is TRADENAME 30 micrograms/dose dispersion for injection, please refer to the handling instructions for TRADENAME (Do Not Dilute). • If the plastic cap and border around the label have another color, such as purple, orange, or maroon, please refer to the handling instructions of these TRADENAME vaccines.
HANDLING PRIOR	
 **Store in the refrigerator for up to 10 weeks prior to use.**	• If the multidose vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 10 vial pack may take 6 hours to thaw. Ensure vials are completely thawed prior to use. • Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton. • Unopened vials can be stored for up to 10 weeks at 2 °C to 8 °C; not exceeding the printed expiry date (EXP). • Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C. • Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

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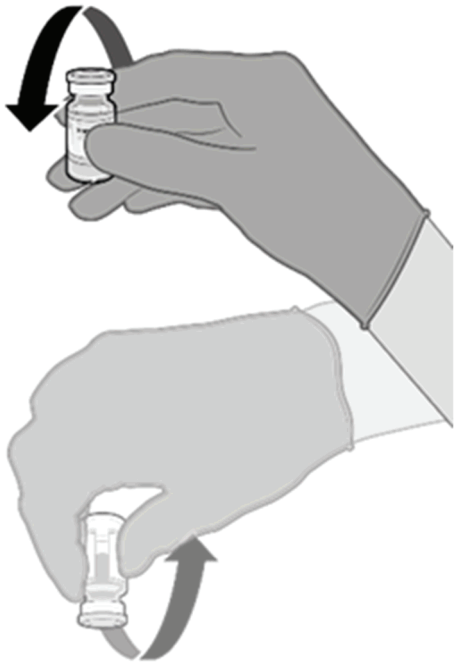 **Gently × 10**	• Gently mix by inverting vials 10 times prior to use. Do not shake. • Prior to mixing, the thawed dispersion may contain white to off-white opaque amorphous particles. • After mixing, the vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the vaccine if particulates or discolouration are present.

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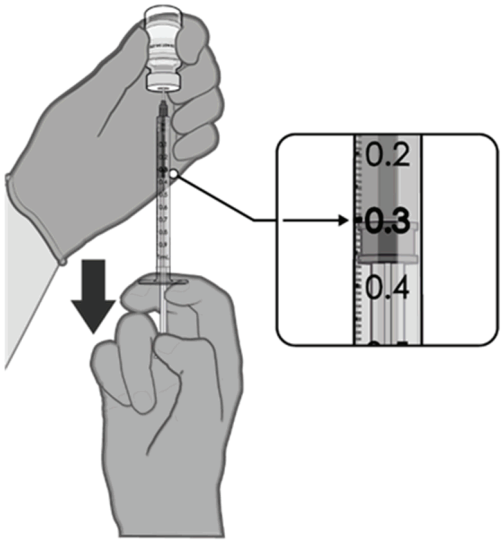
PREPARATION OF INDIVIDUAL 0.3 mL DOSES OF TRADENAME (Bivalent)	
 **Withdraw 0.3 mL dose of vaccine.**	• Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab. • Withdraw 0.3 mL of TRADENAME (Bivalent). Low dead-volume syringes and/or needles should be used in order to extract 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. • Record the appropriate date/time on the vial. Discard any unused vaccine 12 hours after first puncture.

Disposal

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

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7. REFERENCES

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

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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

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41. Module 2.7.4 Summary of Clinical Safety, MAA Type II Variation (12-15 Years) Table 6: Demographic Characteristics – Subjects 12 Through 15 and 16 Through 25 Years of Age – Safety Population
42. Table: Follow-up Time After Dose 2 – Subjects 12 Through 15 Years of Age – Safety Population
43. Table: Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population
44. Table: Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population
45. Table: Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 Through 1 Month After Dose 2, by System Organ Class and Preferred Term – Subjects 12 Through 15 and 16 Through 25 Years of Age (Reactogenicity Subset) – Safety Population
46. Table: Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-up Period – Subjects 12 Through 15 Years of Age and Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
47. Table: Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-up Period – Subjects 12 Through 15 Years of Age and With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
48. Table: Summary of Geometric Mean Ratio – NT50 – Comparison of Subjects 12 Through 15 Years of Age to Subjects 16 Through 25 Years of Age (Immunogenicity Subset) – Subjects Without Evidence of Infection up to 1 Month After Dose 2 – Dose 2 Evaluable Immunogenicity Population
49. Module 2.7.4 Summary of Clinical Safety, COVID-19 Vaccine – MAA Type II Variation (12-15 Years) April 2021
50. Interim Report – 6 Month Update: A Phase 1/2/3, Placebo-Controlled, Randomized, Observer-Blind, Dose-Finding Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of SARS-COV-2 RNA Vaccine Candidates Against COVID-19 in Healthy Individuals [hereafter Interim Report – 6 Month Update] (13 March 2021), Supplemental Table 14.198 Demographic Characteristics, by Age Groups – Phase 2/3 Subjects ≥16 Years of Age – Safety Population
51. Interim Report – 6 Month Update (13 March 2021), Supplemental table 14.84 – Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2 – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 HIV Positive Subjects ≥16 Years of Age – Safety Population
52. Final Analysis Interim Report: A Phase 1/2/3, Placebo-Controlled, Randomized, Observer-Blind, Dose-Finding Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of SARS-COV-2 RNA Vaccine Candidates Against COVID-19 in Healthy

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Individuals (04 November 2020), Section 10.3.3 Phase 2/3, Table 8 Vaccine Administration Timing – ~38000 Subjects for Phase 2/3 Analysis – All Randomized Subjects

53. Interim Report – 6 Month Update (13 March 2021), Table 19. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Subgroup – Blinded Placebo-Controlled Follow-up Period – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
54. Interim Report – 6 Month Update (13 March 2021), Supplemental Table 14.59. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Subgroup– Blinded Placebo-Controlled Follow-up Period–Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
55. Interim Report – 6 Month Update (13 March 2021), Table 20. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – Blinded Placebo-Controlled Follow-up Period – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
56. Interim Report – 6 Month Update (13 March 2021), Table 21. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – Blinded Placebo-Controlled Follow-up Period – Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
57. Interim Report – 6 Month Update (13 March 2021), Table 25. Vaccine Efficacy – First Severe COVID-19 Occurrence From 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-up Period – Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
58. Interim Report – 6 Month Update (13 March 2021), Table 26. Vaccine Efficacy – First Severe COVID-19 Occurrence After Dose 1 – Blinded Placebo-Controlled Follow-up Period – Dose 1 All-Available Efficacy Population
59. Interim Report – 6 Month Update (13 March 2021), Supplemental Table 14.61. Vaccine Efficacy – First Severe COVID-19 Occurrence Based on CDC-Definition After Dose 1 – Blinded Placebo-Controlled Follow-up Period – Dose 1 All-Available Efficacy Population
60. Interim Report – 6 Month Update (13 March 2021), Table 28. Vaccine Efficacy – First Severe COVID-19 Occurrence Based on CDC-Definition From 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-up Period – Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population
61. EUA Amendment for Pfizer-BioNTech COVID-19 Vaccine, 6-Month Follow-Up Data from Participants 16 Years of Age and Older (13 March 2021), Section 6.2.1.2.1.2 Efficacy
62. Interim Report – 6 Month Update (13 March 2021), Table 4. Analysis Populations
63. Module 3.2.P.8.1 Stability Summary and Conclusion, August 2021
64. Adverse Drug Reaction Frequency Justification Document, COVID-19 Vaccine (BNT162B2), August 2022
65. Interim Report – 6 Month Update (13 March 2021), Supplemental Table 14.72 – Local Reactions, by Maximum Severity, Within 7 Days After Each Dose (Reactogenicity Subset)

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

66. Interim Report – 6 Month Update (13 March 2021), Supplemental Table 14.79 – Systemic Events, by Maximum Severity, Within 7 Days After Each Dose (Reactogenicity Subset) – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 HIV-Positive Subjects ≥16 Years of Age – Safety Population
67. 2.5 Clinical Overview to Support Inclusion of Vaccine Stress-Related Reactions in Section 4.4 of the Core Data Sheet, May 2021
68. EUA Amendment for Pfizer-BioNTech COVID-19 Vaccine, 6-Month Follow-Up Data from Participants 16 Years of Age and Older (13 March 2021), Section 6.2.2.1.1 Study Populations – BNT162-01 Phase 1 Participants
69. 2.5 Clinical Overview to Support Inclusion of Myocarditis & Pericarditis in Section 4.4 (Special Warnings and Precautions for use) of the Core Data Sheet, July 2021
70. Module 3.2.P.8.3 Stability Data, August 2021
71. Interim Report – BNT162b2 Booster (Dose 3): A Phase 1/2/3, Placebo Controlled, Randomized, Observer-Blind, Dose-Finding Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of SARS-CoV-2 RNA Vaccine Candidates Against COVID-19 in Healthy Individuals
72. Module 3.2.P.2.2 Drug Product – Tris-Sucrose, September 2021
73. Interim Report – Children 5 to <12 Years of Age: A Phase 1, Open-Label Dose-Finding Study to Evaluate Safety, Tolerability, and Immunogenicity and Phase 2/3 Placebo-Controlled, Observer-Blinded Safety, Tolerability, and Immunogenicity Study of a SARS-CoV-2 RNA Vaccine Candidate against COVID-19 in Healthy Children and Young Adults
74. Module 3.2.P.1 Description and Composition of the Drug Product – Tris-Sucrose, September 2021
75. Module 3.2.P.8.1 Stability Summary and Conclusion – Tris-Sucrose, September 2021
76. Module 3.2.P.3.5 Shipping Validation – Tris-Sucrose, September 2021
77. Module 3.2.P.2.6 Compatibility – Tris-Sucrose, September 2021
78. Module 3.2.P.2.3 Manufacturing Process Development – Process Development and Characterization – Tris/Sucrose, September 2021
79. Module 3.2.P.8.1 Stability Summary and Conclusions – Tris-Sucrose, November 2021
80. 2.5 Clinical Overview for Adult Booster Efficacy MAA – Study C4591031, November 2021
81. Interim Clinical Study Report, Protocol C4591001 – Interim Report – Adolescent 6-Month Update: A Phase 1/2/3, Placebo-Controlled, Randomized, Observer-Blind, Dose-Finding Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of SARS-CoV-2 mRNA Vaccine Candidates Against COVID-19 in Healthy Individuals
82. Clinical Information Amendment – COVID-19 Vaccine C4591007 (5 to <12 Years) Efficacy Data in Phase 2/3 Study C4591007, October 2021

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83. Module 3.2.P.8.3 Stability Data, August 2021
84. 2.5 Clinical Overview – Pediatric (5-12 Years) Booster MAA Extension – April 2022
85. Module 3.2.P.2.2 Drug Product – Tris-Sucrose, May 2022
86. 2.5 Clinical Overview – Pediatric (6m-5y) Three-Dose Series MAA Extension - June 2022
87. 2.5 Clinical Overview – BNT162b2 30 mcg Adult Booster (Dose 3) sBLA_MAA – May 2022 - 2.5.1.2.4 Proposed Indication
88. 2.5 Clinical Overview – Pediatric (6m-5y) Three-Dose Series MAA Extension - June 2022 - 2.5.1.2.3.2.2 Phase 1/2/3 Study C4591007
89. 2.5 Clinical Overview – To Support Inclusion of Myocarditis and Pericarditis as Adverse Drug Reactions in Section 4.8 of the Core Data Sheet – July 2022
90. 2.5 Clinical Overview – Pediatric (6m-5y) Three-Dose Series MAA Extension - June 2022 – Table 41. Disposition of All Randomized Participants Prior to Unblinding – Phase 2/3 – 2 to <5 Years of Age, Table 40. Follow-Up Time After Dose 2 or Dose 3 – Phase 2/3 – 2 to <5 Years of Age – Safety Population
91. Module 5 Table: Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Phase 2/3 – Blinded Placebo-Controlled Follow-Up Period – 2 to <5 Years of Age – Safety Population
92. Module 5 Table: Systemic Events, by Maximum Severity, Within 7 days After Each Dose – Phase 2/3 – Blinded Placebo-Controlled Follow-Up Period – 2 to <5 Years of Age – Safety Population
93. 2.5 Clinical Overview – Pediatric (6m-5y) Three-Dose Series MAA Extension - June 2022 - Table 50. Disposition of All Randomized Participants Prior to Unblinding – Phase 2/3 – 6 Months to <2 Years of Age
94. Module 5 Table: Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Phase 2/3 – Blinded Placebo-Controlled Follow-Up Period – 6 Months to <2 Years of Age – Safety Population
95. Module 5 Table: Systemic Events, by Maximum Severity, Within 7 days After Each Dose – Phase 2/3 – Blinded Placebo-Controlled Follow-Up Period – 6 Months to <2 Years of Age – Safety Population
96. Interim Clinical Study Report – C4591001 – 19 May 2022 - Table 12. Follow-up Time After Booster Dose – Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 μg)
97. 2.5 Clinical Overview – BNT162b2 30 mcg Adult Booster (Dose 3)_sBLA_MAA – May 2022 - 2.5.4.4.2.1.2 Duration of Follow-Up – C4591031 – 6 Months Post-Dose 3
98. Interim Full Clinical Study Report – C4591031 Substudy A - 6 Month Analysis – 07 June 2022 – Table 10. Follow-Up Time After Booster Vaccination – Safety Population
99. 2.5 Clinical Overview – Pediatric (6m-5y) Three-Dose Series MAA Extension - June 2022 - Table 28. Demographic Characteristics – Phase 2/3 – 2 to <5 Years of Age – Dose 3 All-Available Efficacy Population

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100. 2.5 Clinical Overview – Pediatric (6m-5y) Three-Dose Series MAA Extension - June 2022 - Table 29. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 3 – Blinded Follow-Up Period – Phase 2/3 – 2 to <5 Years of Age – Dose 3 All-Available Efficacy Population
101. 2.5 Clinical Overview – Pediatric (6m-5y) Three-Dose Series MAA Extension - June 2022 – Table 7. Demographic Characteristics – Immunobridging Subset – Participants Without Evidence of Infection – Study C4591007 Phase 2/3 2 to <5 Years of Age and Study C4591001 Phase 2/3 16 Through 25 Years of Age – Evaluable Immunogenicity Population
102. 2.5 Clinical Overview – Pediatric (6m-5y) Three-Dose Series MAA Extension - June 2022 - Table 8. Summary of Geometric Mean Ratios – NT50 – Participants Without Evidence of Infection – Immunobridging Subset – Study C4591007 Phase 2/3 2 to <5 Years of Age (1 Month After Dose 3) and Study C4591001 Phase 2/3 16 Through 25 Years of Age (1 Month After Dose 2) – Evaluable Immunogenicity Population
103. 2.5 Clinical Overview – Pediatric (6m-5y) Three-Dose Series MAA Extension - June 2022 - Table 9. Difference in Percentages of Participants With Seroresponse – Participants Without Evidence of Infection – Immunobridging Subset – Comparison of Study C4591007 Phase 2/3 2 to <5 Years of Age (1 Month After Dose 3) and Study C4591001 Phase 2/3 16 Through 25 Years of Age (1 Month After Dose 2) – Evaluable Immunogenicity Population
104. 2.5 Clinical Overview – Pediatric (6m-5y) Three-Dose Series MAA Extension - June 2022 - Table 34. Demographic Characteristics – Phase 2/3 – 6 Months to <2 Years of Age – Dose 3 All-Available Efficacy Population
105. 2.5 Clinical Overview – Pediatric (6m-5y) Three-Dose Series MAA Extension - June 2022 - Table 35. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 3 – Blinded Follow-Up Period – Phase 2/3 – 6 Months to <2 Years of Age – Dose 3 All-Available Efficacy Population
106. 2.5 Clinical Overview – Pediatric (6m-5y) Three-Dose Series MAA Extension - June 2022 – Table 17. Demographic Characteristics – Immunobridging Subset – Participants Without Evidence of Infection – Study C4591007 Phase 2/3 6 Months to <2 Years of Age and Study C4591001 Phase 2/3 16 Through 25 Years of Age – Evaluable Immunogenicity Population
107. 2.5 Clinical Overview – Pediatric (6m-5y) Three-Dose Series MAA Extension - June 2022 – Table 18. Summary of Geometric Mean Ratios – NT50 – Participants Without Evidence of Infection – Immunobridging Subset – Study C4591007 Phase 2/3 6 Months to <2 Years of Age (1 Month After Dose 3) and Study C4591001 Phase 2/3 16 Through 25 Years of Age (1 Month After Dose 2) – Evaluable Immunogenicity Population
108. 2.5 Clinical Overview – Pediatric (6m-5y) Three-Dose Series MAA Extension - June 2022 – Table 19. Difference in Percentages of Participants With Seroresponse – Participants Without Evidence of Infection – Immunobridging Subset – Comparison of Study C4591007 Phase 2/3 6 Months to <2 Years of Age (1 Month After Dose 3) and Study C4591001 Phase 2/3 16 Through 25 Years of Age (1 Month After Dose 2) – Evaluable Immunogenicity Population
109. Module 5.3.5.1. Table: Geometric Mean Ratio – Comparison of 1 Month After Booster Dose to 1 Month After Dose 2 – Phase 3 – BNT162b2 – Experienced Subjects Without

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Evidence of Infection up to 1 Month After Booster Dose Who Were Rerandomized to Receive 1 Booster Dose (30 ug) – Dose 3 Booster Evaluable Immunogenicity Population

110. Interim Clinical Study Report – C4591001 – 19 May 2022 – Table 4 Analysis Populations
111. Module 5.3.5.1. Table: Percentage Difference of Subjects Achieving Seroresponse – Comparison of 1 Month After Booster Dose to 1 Month After Dose 2 – Phase 3 – BNT162b2 – Experienced Subjects Without Evidence of Infection up to 1 Month After Booster Dose Who Were Rerandomized to Receive 1 Booster Dose (30 ug) – Dose 3 Booster Evaluable Immunogenicity Population
112. 2.5 Clinical Overview – BNT162b2 30 mcg Adult Booster (Dose 3) sBLA_MAA – May 2022 – 2.5.4.4.2.5 Efficacy Conclusions – C4591031 – 6 Months Post-Dose 3
113. 2.5 Clinical Overview – BNT162b2 30 mcg Adult Booster (Dose 3) sBLA_MAA – May 2022 – 2.5.4.4.2.1.2 Duration of Follow-Up - C4591031 - 6 Month Post-Dose 3, Table 14. Follow-Up Time After Booster Vaccination – Participants Without Evidence of Infection Prior to 7 Days After Booster Vaccination – Evaluable Efficacy Population
114. 2.5 Clinical Overview – BNT162b2 30 mcg Adult Booster (Dose 3) sBLA_MAA – May 2022 – 2.5.4.4.2.2 Confirmed COVID-19 Cases – C4591031 – 6 Months Post-Dose 3, Table 16. Vaccine Efficacy - First COVID-19 Occurrence From 7 Days After Booster Vaccination – Blinded Follow-Up Period – Participants Without Evidence of Infection Prior to 7 Days After Booster Vaccination – Evaluable Efficacy Population
115. 2.5 Clinical Overview – BNT162b2 30 mcg Adult Booster (Dose 3) sBLA_MAA – May 2022 – 2.5.4.4.2.2 Confirmed COVID-19 Cases – C4591031 – 6 Months Post-Dose 3, Table 17. Vaccine Efficacy - First COVID-19 Occurrence From 7 Days After Booster Vaccination – Blinded Follow-Up Period – Participants With or Without Evidence of Infection Prior to 7 Days After Booster Vaccination – Evaluable Efficacy Population
116. Module 3.2.P.1 Description and Composition of the Drug Product – Tris-Sucrose – May 2022
117. Module 3.2.P.3.5 Process Validation and/or Evaluation – Shipping Validation – June 2022
118. Module 3.2.P.8.1 Stability Summary and Conclusion – Tris-Sucrose – May 2022
119. Module 3.2.P.2.6 Compatibility – Tris-Sucrose – May 2022
120. Module 3.2.S.1.1 Nomenclature, Omicron BA.4/BA.5 – July 2022
121. 2.5 Clinical Overview – BNT162b2– Omicron Modified Vaccine (C4591031 SSE)_MAA_July 2022 – 2.5.6.3 Benefit-Risk Conclusions
122. Interim Full Clinical Study Report – Protocol C4591031 Substudy D: Substudy D Interim Report – Cohort 2 – 1-Month Analysis: A Phase 3 Master Protocol to Evaluate Additional Dose(s) of BNT162b2 in Healthy Individuals Previously Vaccinated With BNT162b2 – Section 3.1 Overview of Study Design - 10 June 2022
123. Interim Full Clinical Study Report – Protocol C4591031 Substudy D: Substudy D Interim Report – Cohort 2 – 1-Month Analysis: A Phase 3 Master Protocol to Evaluate Additional Dose(s) of BNT162b2 in Healthy Individuals Previously Vaccinated With BNT162b2 – Section 4.1 Disposition of Participants – Cohort 2 - 10 June 2022

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124. Interim Full Clinical Study Report – Protocol C4591031 Substudy D – Section 4.7 Duration of Follow-UP - 10 June 2022
125. Interim Full Clinical Study Report – Protocol C4591031 Substudy D: Substudy D Interim Report – Cohort 2 – 1-Month Analysis: A Phase 3 Master Protocol to Evaluate Additional Dose(s) of BNT162b2 in Healthy Individuals Previously Vaccinated With BNT162b2 – Section 5.2.1. Local Reactions - 10 June 2022
126. Interim Full Clinical Study Report – Protocol C4591031 Substudy D: Substudy D Interim Report – Cohort 2 – 1-Month Analysis: A Phase 3 Master Protocol to Evaluate Additional Dose(s) of BNT162b2 in Healthy Individuals Previously Vaccinated With BNT162b2 – Section 5.2.2. Systemic Events - 10 June 2022
127. Interim Full Clinical Study Report – Protocol C4591031 Substudy E – Table 7. Demographic Characteristics – Expanded Cohort – Participants >55 Years of Age – Safety Population - 16 July 2022
128. Interim Full Clinical Study Report – Protocol C4591031 Substudy E – Table 5. Follow-up Time After Study Vaccination – Expanded Cohort – Participants >55 Years of Age – Safety Population - 16 July 2022
129. Interim Full Clinical Study Report – Protocol C4591031 Substudy E – Section 5.1.2.3.1.2 Adverse Events from Study Vaccination to Data Cutoff Date - 16 July 2022
130. Interim Full Clinical Study Report – Protocol C4591031 Substudy E – Table 21. Number (%) of Participants Reporting at Least 1 Adverse Event From the Study Vaccination Through 1 Month After the Study Vaccination, by System Organ Class and Preferred Term — Expanded Cohort — Participants >55 Years of Age — Safety Population – 16 July 2022
131. Interim Full Clinical Study Report – Protocol C4591031 Substudy E – Supplemental Table 14.38 Systemic Events, by Maximum Severity, Within 7 Days After the Study Vaccination – Expanded Cohort – Participants >55 Years of Age – Safety Population - 16 July 2022
132. Interim Full Clinical Study Report – Protocol C4591031 Substudy E – Supplemental Table 14.26 Local Reactions, by Maximum Severity, Within 7 Days After the Study Vaccination – Expanded Cohort – Participants >55 Years of Age – Safety Population - 16 July 2022
133. 2.5 Clinical Overview – BNT162b2– Omicron Modified Vaccine (C4591031 SSE)_MAA_July 2022 – Section 2.5.1.2.3.2.1. Study C4591031 Substudy E
134. 2.5 Clinical Overview – BNT162b2– Omicron Modified Vaccine (C4591031 SSE)_MAA_July 2022 – Section 2.5.5.2.1.1. Safety Population Characteristics – C4591031 Substudy E (Expanded Cohort)
135. Module 5.3.5.1 – Table – Demographic Characteristics – Expanded Cohort – Participants >55 Years of Age – Safety Population
136. 2.5 Clinical Overview – BNT162b2– Omicron Modified Vaccine (C4591031 SSE)_MAA_July 2022 – 2.5.5.2.1.3.1. Overview of Adverse Events
137. 2.5 Clinical Overview – BNT162b2– Omicron Modified Vaccine (C4591031 SSE)_MAA_July 2022 – 2.5.5.2.1.3.1.1. Adverse Events by System Organ Class and Preferred Term, Adverse Events from Study Vaccination to Data Cutoff Date

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138. 2.5 Clinical Overview – BNT162b2– Omicron Modified Vaccine (C4591031 SSE)_MAA_July 2022 – 2.5.5.2.1.2. Reactogenicity – C4591031 Substudy E (Expanded Cohort)

139. 2.5 Clinical Overview – BNT162b2– Omicron Modified Vaccine (C4591031 SSE)_MAA_July 2022 – 2.5.5.2.1.8. Safety Conclusions – C4591031 Substudy E

140. Interim Full Clinical Study Report – Protocol C4591031 Substudy E – Table 7. Demographic Characteristics – Expanded Cohort – Participants >55 Years of Age – Safety Population - 16 July 2022

141. 2.5 Clinical Overview – BNT162b2– Omicron Modified Vaccine (C4591031 SSE)_MAA_July 2022 – 2.5.1.1.1.1. Immunogenicity Endpoints and Analysis Methods – C4591031 Substudy E, Immunogenicity Analysis Methods - C4591031 Substudy E

142. 2.5 Clinical Overview – BNT162b2– Omicron Modified Vaccine (C4591031 SSE)_MAA_July 2022 – 2.5.4.2.1.2.1.1. GMR of Omicron BA.1 Neutralizing Titres

143. 2.5 Clinical Overview – BNT162b2– Omicron Modified Vaccine (C4591031 SSE)_MAA_July 2022 – Table 4. Difference in Percentages of Participants With Seroresponse – Participants Without Evidence of Infection up to 1 Month After the Study Vaccination – Expanded Cohort – Immunogenicity Subset – Participants >55 Years of Age – Evaluable Immunogenicity Population

144. 2.5 Clinical Overview – BNT162b2– Omicron Modified Vaccine (C4591031 SSE)_MAA_July 2022 – Table 2. Geometric Mean Ratios For Between Vaccine Group Comparison – Participants Without Evidence of Infection up to 1 Month After the Study Vaccination – Expanded Cohort – Immunogenicity Subset – Participants >55 Years of Age – Evaluable Immunogenicity Population

145. 2.5 Clinical Overview – BNT162b2– Omicron Modified Vaccine (C4591031 SSE)_MAA_July 2022 – Table 4. Difference in Percentages of Participants With Seroresponse – Participants Without Evidence of Infection up to 1 Month After the Study Vaccination – Expanded Cohort – Immunogenicity Subset – Participants >55 Years of Age – Evaluable Immunogenicity Population

146. Interim Full Clinical Study Report – Protocol C4591031 Substudy D: Substudy D Interim Report – Cohort 2 – 1-Month Analysis: A Phase 3 Master Protocol to Evaluate Additional Dose(s) of BNT162b2 in Healthy Individuals Previously Vaccinated With BNT162b2 – Table 4. Disposition of All Randomized Participants - Cohort 2 - 10 June 2022

147. Interim Full Clinical Study Report – Protocol C4591031 Substudy D: Substudy D Interim Report – Cohort 2 – 1-Month Analysis: A Phase 3 Master Protocol to Evaluate Additional Dose(s) of BNT162b2 in Healthy Individuals Previously Vaccinated With BNT162b2 – Section 3.1. Overview of Study Design - 10 June 2022

148. Interim Full Clinical Study Report – Protocol C4591031 Substudy D: Substudy D Interim Report – Cohort 2 – 1-Month Analysis: A Phase 3 Master Protocol to Evaluate Additional Dose(s) of BNT162b2 in Healthy Individuals Previously Vaccinated With BNT162b2 – Section 5.1.1.1. Superiority Analysis - GMR of Omicron-Neutralizing Titers in BNT162b2 OMI Dose 4 Recipients Compared to BNT162b2 Dose 4 Recipients - 10 June 2022

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149. Interim Full Clinical Study Report – Protocol C4591031 Substudy D: Substudy D Interim Report – Cohort 2 – 1-Month Analysis: A Phase 3 Master Protocol to Evaluate Additional Dose(s) of BNT162b2 in Healthy Individuals Previously Vaccinated With BNT162b2 – Table 11 - 10 June 2022

150. Interim Full Clinical Study Report – Protocol C4591031 Substudy D: Substudy D Interim Report – Cohort 2 – 1-Month Analysis: A Phase 3 Master Protocol to Evaluate Additional Dose(s) of BNT162b2 in Healthy Individuals Previously Vaccinated With BNT162b2 – Section 5.4.1. Immunogenicity, Descriptive Immunogenicity Analyses – Full Expanded Set - 10 June 2022

151. Interim Full Clinical Study Report – Protocol C4591031 Substudy D: Substudy D Interim Report – Cohort 2 – 1-Month Analysis: A Phase 3 Master Protocol to Evaluate Additional Dose(s) of BNT162b2 in Healthy Individuals Previously Vaccinated With BNT162b2 – Table 10 - 10 June 2022

152. Module 3.2.P.1 Description and composition of the drug product – July 2022

153. Module 3.2.P.2.3 Process development and characterization – July 2022

154. 2.5 Clinical Overview – BNT162b2– Omicron Modified Vaccine (C4591031 SSE)_MAA_July 2022 – 2.5.4.2.1.2.1.2. Seroresponse Rate to Omicron BA.1 Strain

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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)

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)[64]

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

a. Source: Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2, by System Organ Class and Preferred Term – Blinded Placebo-Controlled Follow-up Period – Phase 2/3 Subjects ≥16 Years of Age – Safety Population (Study C4591001, Cut-off 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 (Study C4591001, Cut-off 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 (Study C4591001, Cut-off date: 13March2021).
d. These adverse reactions were identified in the post-authorization period.
e. Due to the cross-over design of clinical trials, the actual incidence of myocarditis and pericarditis cannot be reliably estimated however, based on published literature presented in the Clinical Overview, the CIOMS frequency category for myocarditis and pericarditis is "very rare."[89]

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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)[64]

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]	
Cardiac disorders	Myocarditis[d]	N/A[f]
	Pericarditis[d]	N/A[f]
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 (Study C4591001, Cut-off 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 (Study C4591001, Cut-off 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 (Study C4591001, Cut-off date: 13March2021).
d. These adverse reactions were identified in the post-authorization period.
e. The following reactions were not reported in the 12 through 15 year old age group in Study C4591001: angioedema, pruritus, malaise, lethargy, asthenia, decreased appetite, hyperhidrosis, and night sweats but are still considered adverse reactions for this age group.
f. Due to the cross-over design of clinical trials, the actual incidence of myocarditis and pericarditis cannot be reliably estimated however, based on published literature presented in the Clinical Overview, the CIOMS frequency category for myocarditis and pericarditis is "very rare."[89]

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Table A-3. Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency within each System Organ Class: Individuals 5 Through <12 Years of Age (06 September 2021 Data Cut-off Date)[64]

System Organ Class	ADR Term	Frequency n/N (%)
Blood and lymphatic system disorders	Lymphadenopathy	13/1518 (0.9%)[a]
Immune system disorders	Anaphylaxis[d]	Not known
	Hypersensitivity reactions	
	Rash[d]	5/1518 (0.3%)[a]
	Urticaria[d]	3/1518 (0.2%)[a]
	Pruritus[d]	1/1518 (0.1%)[a]
	Angioedema[d,e]	
Metabolism and nutrition disorders	Decreased appetite	1/1518 (0.1%)[a]
Nervous system disorders	Headache	579/1517 (38.2%)[b]
	Lethargy[e]	
Cardiac disorders	Myocarditis[d,e]	N/A[f]
	Pericarditis[d,e]	N/A[f]
Gastrointestinal disorders	Diarrhea[d]	146/1517 (9.6%)[b]
	Vomiting[d]	60/1517 (4.0%)[b]
	Nausea	6/1518 (0.4%)[a]
Skin and subcutaneous tissue disorders	Hyperhidrosis[e]	
	Night sweats[e]	
Musculoskeletal and connective tissue disorders	Myalgia (muscle pain)	266/1517 (17.5%)[b]
	Arthralgia (joint pain) (new)	115/1517 (7.6%)[b]
	Pain in extremity (arm)[d]	3/1518 (0.2%)[a]
General disorders and administration site conditions	Injection site pain	1279/1517 (84.3%)[c]
	Fatigue	785/1517 (51.7%)[b]
	Injection site redness	401/1517 (26.4%)[c]
	Injection site swelling	309/1517 (20.4%)[c]
	Chills	188/1517 (12.4%)[b]
	Pyrexia	126/1517 (8.3%)[b]
	Malaise	2/1518 (0.1%)[a]
	Asthenia[e]	

a. Source: Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2, by System Organ Class and Preferred Term – Phase 2/3 – 5 to <12 Years of Age – Safety Population (Study C4591007, Cut-off date: 06Sep2021).
b. Source: Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Phase 2/3 – 5 to <12 Years of Age – Safety Population (Study C4591007, Cut-off date: 06Sep2021).
c. Source = Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Phase 2/3 – 5 to <12 Years of Age – Safety Population (Study C4591007, Cut-off date: 06Sep2021).
d. These adverse reactions were identified in the post-authorization period.
e. At the time of the data cut-off date, the following reactions were not reported in participants 5 through <12 years of age in Study C4591007: **Error! Reference source not found.**angioedema, lethargy, myocarditis, pericarditis, asthenia, hyperhidrosis, and night sweats but are still considered adverse reactions for this age group.
f. Due to the cross-over design of clinical trials, the actual incidence of myocarditis and pericarditis cannot be reliably estimated however, based on published literature presented in the Clinical Overview, the CIOMS frequency category for myocarditis and pericarditis is "very rare."[89]

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Table A-4. Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency Within Each System Organ Class: Individuals 2 to <5 Years of Age (29 April 2022 Data Cut-off Date)[64]

System Organ Class	ADR Term	Frequency n/N (%)
Blood and lymphatic system disorders	Lymphadenopathy	1/1835 (0.1%)[a]
Immune system disorders	Anaphylaxis[d]	Not known
	Hypersensitivity reactions	
	Rash[d,e]	6/1835 (0.3%)[a]
	Urticaria[d]	6/1835 (0.3%)[a]
	Pruritis[d,f]	
	Angioedema[d,f]	
Metabolism and nutrition disorders	Decreased appetite	1/1835 (0.1%)[a]
Nervous system disorders	Headache	159/1826 (8.7%)[b]
	Lethargy[f]	
Cardiac disorders	Myocarditis[d,f]	N/A[g]
	Pericarditis[d,f]	N/A[g]
Gastrointestinal disorders	Diarrhea[d]	248/1826 (13.6%)[b]
	Vomiting[d]	117/1826 (6.4%)[b]
	Nausea	2/1835 (0.1%)[a]
Skin and subcutaneous tissue disorders	Hyperhidrosis[f]	
	Night sweats[f]	
Musculoskeletal and connective tissue disorders	Myalgia (muscle pain)	92/1826 (5.0%)[b]
	Arthralgia (joint pain) (new)	44/1826 (2.4%)[b]
	Pain in extremity (arm)[d]	3/1835 (0.2%)[a]
General disorders and administration site conditions	Injection site pain	858/1826 (47.0%)[c]
	Fatigue	818/1826 (44.8%)[b]
	Injection site redness	346/1833 (18.9%)[c]
	Pyrexia	192/1832 (10.5%)[b]
	Injection site swelling	154/1833 (8.4%)[c]
	Chills	104/1826 (5.7%)[b]
	Asthenia	1/1835 (0.1%)[a]
	Malaise[f]	

a. Source: Number (%) of Participants Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 3, by System Organ Class and Preferred Term – Phase 2/3 – Blinded Placebo-Controlled Follow-Up Period – 2 to <5 Years of Age – Safety Population (Study C4591007, Cutoff date: 29Apr2022)
b. Source = Systemic Events, by Maximum Severity, Within 7 Days After Each Dose –Phase 2/3 – Blinded Placebo Controlled Follow-Up Period – 2 to <5 Years of Age – Safety Population (Study C4591007, Cutoff date: 06Sep2021)
c. Source = Local Reactions, by Maximum Severity, Within 7 Days After Each Dose –Phase 2/3 – Blinded Placebo-Controlled Follow-Up Period – 2 to <5 Years of Age – Safety Population (Study C4591007, Cutoff date: 29Apr2022)
d. These adverse reactions were identified in the post-authorization period.
e. The frequency of rash was calculated as follows: Rash (n=4), Rash erythematous (n=1), Rash maculo-papular (n=1) (4+1+1=6/1835=0.3%).
f. At the time of the data-lock the following reactions were not reported in participants 2 to <5 Years of Age in Study C4591007: pruritus, angioedema, lethargy, myocarditis, pericarditis, hyperhidrosis, night sweats, and malaise but are still considered adverse reactions for this age group.
g. Due to the cross-over design of clinical trials, the actual incidence of myocarditis and pericarditis cannot be reliably estimated however, based on published literature presented in the Clinical Overview, the CIOMS frequency category for myocarditis and pericarditis is "very rare."[89]

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Table A-5. Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency Within Each System Organ Class: Individuals 6 Months to <2 Years of Age (29 April 2022 Data Cut-off Date)[64]

System Organ Class	ADR Term	Frequency n/N (%)
Blood and lymphatic system disorders	Lymphadenopathy	2/1178 (0.2%)[a]
Immune system disorders	Anaphylaxis[d]	Not known
	Hypersensitivity reactions	
	Rash[d,e]	13/1178 (1.1%)[a]
	Urticaria[d]	8/1178 (0.7%)[a]
	Pruritis[d,f]	
	Angioedema[d,f]	
Metabolism and nutrition disorders	Decreased appetite	451/1169 (38.6%)[b]
Psychiatric disorders	Irritability	800/1169 (68.4%)[b]
Nervous system disorders	Headache	2/1178 (0.2%)[a]
	Lethargy	1/1178 (0.1%)[a]
Cardiac disorders	Myocarditis[d,f]	N/A[g]
	Pericarditis[d,f]	N/A[g]
Gastrointestinal disorders	Vomiting[d]	47/1178 (4.0%)[a]
	Diarrhea[d]	39/1178 (3.3%)[a]
	Nausea[f]	
Skin and subcutaneous tissue disorders	Hyperhidrosis[f]	
	Night sweats[f]	
Musculoskeletal and connective tissue disorders	Myalgia (muscle pain)[f]	
	Arthralgia (joint pain) (new)[f]	
	Pain in extremity (arm)[d,f]	
General disorders and administration site conditions	Injection site tenderness	309/1169 (26.4%)[c]
	Injection site redness	210/1177 (17.8%)[c]
	Pyrexia	169/1177 (14.4%)[b]
	Injection site swelling	86/1177 (7.3%)[c]
	Fatigue	8/1178 (0.7%)[a]
	Chills	1/1178 (0.1%)[a]
	Malaise[f]	
	Asthenia[f]	

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Table A-5. Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency Within Each System Organ Class: Individuals 6 Months to <2 Years of Age (29 April 2022 Data Cut-off Date)[64]

a. Source: Number (%) of Participants Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 3, by System Organ Class and Preferred Term – Phase 2/3 – Blinded Placebo-Controlled Follow-Up Period – 6 months to <2 Years of Age – Safety Population (Study C4591007, Cutoff date: 29Apr2022)
b. Source = Systemic Events, by Maximum Severity, Within 7 Days After Each Dose –Phase 2/3 – Blinded Placebo-Controlled Follow-Up Period – 6 months to <2 Years of Age – Safety Population (Study C4591007, Cutoff date: 29Apr2022)
c. Source = Local Reactions, by Maximum Severity, Within 7 Days After Each Dose –Phase 2/3 – Blinded Placebo-Controlled Follow-Up Period – 6 months to <2 Years of Age – Safety Population (Study C4591007, Cutoff date: 29Apr2022)
d. These adverse reactions were identified in the post-authorization period.
e. The frequency of rash was calculated as follows: Rash (n=8), Rash macular (n=1), Rash maculo-papular (n=2); Rash papular (n=1); Rash erythematous (n=1) (8+1+2+1+1=13/1178=1.1%)
f. At the time of the data cut-off date, the following reactions were not reported in participants 6 months to <2 Years of Age in Study C4591007: pruritus, angioedema, myocarditis, pericarditis, nausea, hyperhidrosis, night sweats, myalgia, arthralgia, pain in extremity, malaise, and asthenia but are still considered adverse reactions for this age group.
g. Due to the cross-over design of clinical trials, the actual incidence of myocarditis and pericarditis cannot be reliably estimated however, based on published literature presented in the Clinical Overview, the CIOMS frequency category for myocarditis and pericarditis is “very rare.”[89]

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Table A-6. Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency Within Each System Organ Class: BNT162b2-Experienced Subjects (18 to 55 Years of Age) Who Were Rerandomized to Receive 1 Booster (Dose 3) of BNT162b2 (30 µg) – Booster Safety Population (17 June 2021 Data Cut-off Date)[*,64]

System Organ Class	ADR Term	Frequency n/N (%)
Blood and lymphatic system disorders	Lymphadenopathy	16/306 (5.2%)[a,b]
Immune system disorders	Anaphylaxis[e]	Not known
	Hypersensitivity reactions	
	Rash[e]	1/306 (0.3%)[b]
	Pruritus[e,f]	
	Urticaria[e,f]	
	Angioedema[e,f]	
Metabolism and nutrition disorders	Decreased appetite	1/306 (0.3%)[b]
Nervous system disorders	Headache	140/289 (48.4%)[c]
	Lethargy[f]	
Cardiac disorders	Myocarditis[e]	N/A[g]
	Pericarditis[e]	N/A[g]
Gastrointestinal disorders	Diarrhea[e]	25/289 (8.7%)[c]
	Vomiting[e]	5/289 (1.7%)[c]
	Nausea	2/306 (0.7%)[b]
Skin and subcutaneous tissue disorders	Hyperhidrosis[f]	
	Night sweats[f]	
Musculoskeletal and connective tissue disorders	Myalgia (muscle pain)	113/289 (39.1%)[c]
	Arthralgia (joint pain) (new)	73/289 (25.3%)[c]
	Pain in extremity (arm)[e]	1/306 (0.3%)[b]
General disorders and administration site conditions	Injection site pain	240/289 (83.0%)[d]
	Fatigue	184/289 (63.7%)[c]
	Chills	84/289 (29.1%)[c]
	Pyrexia	25/289 (8.7%)[c]
	Injection site swelling	23/289 (8.0%)[d]
	Injection site redness	17/289 (5.9%)[d]
	Malaise[f]	
	Asthenia[f]	

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

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

b. Source: Number (%) of Subjects Reporting at Least 1 Adverse Event From Booster Dose to 1 Month After Booster Dose, by System Organ Class and Preferred Term – Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) – Booster Safety Population (Study C4591001, Cut-off date: 17June2021).

c. Source = Systemic Events, by Maximum Severity, Within 7 Days After Booster Dose Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) – Booster Safety Population (Study C4591001, Cut-off date: 17June2021).

d. Source = Local Reactions, by Maximum Severity, Within 7 Days After Booster Dose – Phase 3 – BNT162b2-Experienced Subjects Who Were Rerandomized to Receive 1 Booster Dose of BNT162b2 (30 µg) –Booster Safety Population (Study C4591001, Cut-off date: 17June2021).

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

f. The following reactions were not reported in the booster safety population in Study C4591001: angioedema, pruritus, urticaria, malaise, lethargy, asthenia, hyperhidrosis, and night sweats but are still considered adverse reactions.

g. Due to the cross-over design of clinical trials, the actual incidence of myocarditis and pericarditis cannot be reliably estimated however, based on published literature presented in the Clinical Overview, the CIOMS frequency category for myocarditis and pericarditis is “very rare.”[89]

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Table A-7. Adverse Drug Reaction Table of Non-reactogenicity Reactions[a] with Preferred Terms Listed by Decreasing Frequency Within Each System Organ Class: BNT162b2-Experienced Subjects (≥16 Years of Age) Who Received 1 Booster (Dose 3) of BNT162b2 (30 µg) in Study C4591031 Substudy A (SSA) – Booster Safety Population (5 October 2021 Data Cut-off Date)[64,80]

System Organ Class	ADR Term	Frequency n/N (%)
Blood and lymphatic system disorders	Lymphadenopathy[b]	141/5055 (2.8%)[c]
Immune system disorders	Anaphylaxis[d]	Not known
	Hypersensitivity reactions	
	Rash[d]	3/5055 (0.1%)[c]
	Pruritus[d]	3/5055 (0.1%)[c]
	Urticaria[d]	2/5055 (0.04%)[c]
	Angioedema[d,e]	
Metabolism and nutrition disorders	Decreased appetite	9/5055 (0.2%)[c]
Nervous system disorders	Headache[a]	
	Lethargy	12/5055 (0.2%)[c]
Cardiac disorders	Myocarditis[d]	N/A[f]
	Pericarditis[d]	N/A[f]
Gastrointestinal disorders	Diarrhea[a,d]	
	Vomiting[a,d]	
	Nausea	48/5055 (0.9%)[c]
Skin and subcutaneous tissue disorders	Night sweats	5/5055 (0.1%)[c]
	Hyperhidrosis	4/5055 (0.1%)[c]
Musculoskeletal and connective tissue disorders	Myalgia (muscle pain)[a]	
	Arthralgia (joint pain) (new)[a]	
	Pain in extremity (arm)[d]	54/5055 (1.1%)[c]
General disorders and administration site conditions	Injection site pain[a]	
	Fatigue[a]	
	Chills[a]	
	Pyrexia[a,g]	
	Injection site swelling[a]	
	Injection site redness[a]	
	Malaise	35/5055 (0.7%)[c]
	Asthenia	8/5055 (0.2%)[c]

a. Please see Table A-6 for the frequency of the following reactogenicity adverse reactions that were reported in the booster safety population of Study C4591001: headache, diarrhea, vomiting, myalgia (muscle pain), arthralgia (joint pain) (new), injection site pain, fatigue, chills, pyrexia, injection site swelling, injection site redness.
b. A higher frequency of lymphadenopathy (2.8% vs. 0.4%) was observed in participants receiving a booster dose (in Study C4591031) compared to participants receiving 2 doses. The frequency of lymphadenopathy was calculated as follows: Lymphadenopathy (n=135), Lymph node pain (n=4), Lymphadenitis (n=2) (135+4+2=141/5055=2.8%).
c. Source: Number (%) of Participants Reporting at Least 1 Adverse Event From Booster Vaccination to 1 Month After Booster Vaccination, by System Organ Class and Preferred Term – Blinded Follow-up Period – Safety Population (Study C4591031 SSA, Cut-off date: 05October2021).
d. These adverse reactions were identified in the post-authorization period.
e. The following reaction was not reported in the Study C4591031: angioedema but it is still considered an adverse reactions.
f. Due to the cross-over design of clinical trials, the actual incidence of myocarditis and pericarditis cannot be reliably estimated however, based on published literature presented in the Clinical Overview, the CIOMS frequency category for myocarditis and pericarditis is "very rare."[89]
g. The preferred term pyrexia is a cluster term also covering 'body temperature increased'.

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Table A-8. Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency Within Each System Organ Class: Individuals 18 to 55 years old Who Received a Booster (Dose 4) of BNT162b2 30 µg in Study C4591031 Substudy D (SSD) — Safety Population (11 March 2022 Data Cut-off Date)[64]

System Organ Class	ADR Term	Frequency n/N (%)
Blood and lymphatic system disorders	Lymphadenopathy	3/325 (0.9%)[a]
Immune system disorders	Anaphylaxis[b]	
	Hypersensitivity reactions	
	Rash[b,c]	
	Pruritus[b,c]	
	Urticaria[b,c]	
	Angioedema[b,c]	
Metabolism and nutrition disorders	Decreased appetite[c]	
Nervous system disorders	Headache	138/306 (45.1%)[d]
	Lethargy[c]	
Cardiac disorders	Myocarditis[b]	N/A[e]
	Pericarditis[b]	N/A[e]
Gastrointestinal disorders	Diarrhea[b]	36/306 (11.8%)[d]
	Vomiting[b]	5/306 (1.6%)[d]
	Nausea[c]	
Skin and subcutaneous tissue disorders	Hyperhidrosis[c]	
	Night sweats[c]	
Musculoskeletal and connective tissue disorders	Myalgia (muscle pain)	87/306 (28.4%)[d]
	Arthralgia (joint pain) (new)	46/306 (15.0%)[d]
	Pain in extremity (arm)[b,c]	
General disorders and administration site conditions	Injection site pain	240/306 (78.4%)[f]
	Fatigue	185/306 (60.5%)[d]
	Chills	80/306 (26.1%)[d]
	Injection site swelling	27/306 (8.8%)[f]
	Pyrexia	22/306 (7.2%)[d]
	Injection site redness	13/306 (4.2%)[f]
	Malaise[c]	
	Asthenia[c]	

a. Source: Number (%) of Participants Reporting at Least 1 Adverse Event From First Study Vaccination Through 1 Month After First Study Vaccination, by System Organ Class and Preferred Term - Cohort 2 - Safety Population (Study C4591031 SSD, Cutoff date: 11 March 2022)
b. These adverse reactions were identified in the post-authorization period.
c. At the time of the data cut-off date, the following reactions were not reported in the safety population in Study C4591031 SSD: rash, pruritus, urticaria, angioedema, decreased appetite, lethargy, nausea, hyperhidrosis, night sweats, pain in extremity, malaise, and asthenia but are still considered adverse reactions.
d Source = Systemic Events, by Maximum Severity, Within 7 Days After First Study Vaccination - Cohort 2 - Safety Population (Study C4591031 SSD, Cutoff date: 11 March 2022)
e. Due to the cross-over design of clinical trials, the actual incidence of myocarditis and pericarditis cannot be reliably estimated however, based on published literature presented in the Clinical Overview, the CIOMS frequency category for myocarditis and pericarditis is "very rare."[89]
f. Source = Local Reactions, by Maximum Severity, Within 7 Days After First Study Vaccination - Cohort 2 - Safety Population (Study C4591031 SSD, Cutoff date: 11 March 2022)

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Table A-9. Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency Within Each System Organ Class: Individuals >55 years old Who Received a Booster (Dose 4) of BNT162b2 30 µg in Study C4591031 Substudy E (SSE) – Expanded Cohort – Safety Population (16 May 2022 Data Cut-off Date)[64]

System Organ Class	ADR Term	Frequency n/N (%)
Blood and lymphatic system disorders	Lymphadenopathy	1/305 (0.3%)[a]
Immune system disorders	Anaphylaxis[b]	
	Hypersensitivity reactions	
	Rash[b,c]	
	Pruritus[b,c]	
	Urticaria[b,c]	
	Angioedema[b,c]	
Metabolism and nutrition disorders	Decreased appetite[c]	
Nervous system disorders	Headache	79/298 (26.5%)[d]
	Lethargy[c]	
Cardiac disorders	Myocarditis[b]	N/A[e]
	Pericarditis[b]	N/A[e]
Gastrointestinal disorders	Diarrhea[b]	13/298 (4.4%)[d]
	Vomiting[b]	4/298 (1.3%)[d]
	Nausea	1/305 (0.3%)[a]
Skin and subcutaneous tissue disorders	Hyperhidrosis[c]	
	Night sweats[c]	
Musculoskeletal and connective tissue disorders	Myalgia (muscle pain)	59/298 (19.8%)[d]
	Arthralgia (joint pain) (new)	27/298 (9.1%)[d]
	Pain in extremity (arm)[b]	1/305 (0.3%)[a]
General disorders and administration site conditions	Injection site pain	179/298 (60.1%)[f]
	Fatigue	135/298 (45.3%)[d]
	Chills	49/298 (16.4%)[d]
	Injection site redness	19/298 (6.4%)[f]
	Injection site swelling	18/298 (6.0%)[f]
	Pyrexia	11/298 (3.7%)[d]
	Malaise[c]	
	Asthenia[c]	

a. Source: Number (%) of Participants Reporting at Least 1 Adverse Event From the Study Vaccination Through 1 Month After the Study Vaccination, by System Organ Class and Preferred Term — Expanded Cohort — Participants >55 Years of Age — Safety Population (Study C4591031 SSE, Cutoff date: 16 May 2022)
b. These adverse reactions were identified in the post-authorization period.
c. At the time of the data cut-off date, the following reactions were not reported in the safety population in Study C4591031 SSE: rash, pruritus, urticaria, angioedema, decreased appetite, lethargy, hyperhidrosis, night sweats, malaise and asthenia but are still considered ADRs.
d. Source = Systemic Events, by Maximum Severity, Within 7 Days After the Study Vaccination – Expanded Cohort – Participants >55 Years of Age – Safety Population (Study C4591031 SSE, Cutoff date: 16 May 2022)
e. Due to the cross-over design of clinical trials, the actual incidence of myocarditis and pericarditis cannot be reliably estimated however, based on published literature presented in the Clinical Overview, the CIOMS frequency category for myocarditis and pericarditis is "very rare."[89]
f. Source = Local Reactions, by Maximum Severity, Within 7 Days After the Study Vaccination – Expanded Cohort – Participants >55 Years of Age – Safety Population (Study C4591031 SSE, Cutoff date: 16 May 2022)

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Table A-10. Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency Within Each System Organ Class: Individuals 18 to 55 years old Who Received a Booster (Dose 4) of Monovalent BNT162b2 OMI BA.1 (30 ug) in Study C4591031 Substudy D (SSD) – Safety Population (11 March 2022 Data Cut-off Date)[64]

System Organ Class	ADR Term	Frequency n/N (%)
Blood and lymphatic system disorders	Lymphadenopathy[a]	2/315 (0.6%)[b]
Immune system disorders	Anaphylaxis[c]	
	Hypersensitivity reactions	
	Rash[c,d]	
	Pruritus[c,d]	
	Urticaria[c,d]	
	Angioedema[c,d]	
Metabolism and nutrition disorders	Decreased appetite[d]	
Nervous system disorders	Headache	140/294 (47.6%)[e]
	Lethargy[d]	
Cardiac disorders	Myocarditis[c]	N/A[f]
	Pericarditis[c]	N/A[f]
Gastrointestinal disorders	Diarrhea[c]	25/294 (8.5%)[e]
	Vomiting[c]	8/294 (2.7%)[e]
	Nausea[d]	
Skin and subcutaneous tissue disorders	Hyperhidrosis[d]	
	Night sweats	1/315 (0.3%)[b]
Musculoskeletal and connective tissue disorders	Myalgia (muscle pain)	99/294 (33.7%)[e]
	Arthralgia (joint pain) (new)	69/294 (23.5%)[e]
	Pain in extremity (arm)[c,d]	
General disorders and administration site conditions	Injection site pain	229/294 (77.9%)[g]
	Fatigue	189/294 (64.3%)[e]
	Chills	93/294 (31.6%)[e]
	Pyrexia	25/294 (8.5%)[e]
	Injection site swelling	25/294 (8.5%)[g]
	Injection site redness	21/294 (7.1%)[g]
	Malaise[d]	
	Asthenia[d]	

a. The frequency of lymphadenopathy was calculated as follows: Lymphadenopathy (n=1), axillary pain (n=1) (1+1=2/315=0.6%)
b. Source: Number (%) of Participants Reporting at Least 1 Adverse Event From First Study Vaccination Through 1 Month After First Study Vaccination, by System Organ Class and Preferred Term - Cohort 2 - Safety Population (Study C4591031 SSD, Cutoff date: 11 March 2022)
c. These adverse reactions were identified in the post-authorization period.
d. At the time of the data cut-off date, the following reactions were not reported in the safety population in Study C4591031 SSD: rash, pruritus, urticaria, angioedema, decreased appetite, lethargy, nausea, hyperhidrosis, pain in extremity, malaise, and asthenia but are still considered ADRs.
e. Source = Systemic Events, by Maximum Severity, Within 7 Days After First Study Vaccination - Cohort 2 - Safety Population (Study C4591031 SSD, Cutoff date: 11 March 2022)
f. Due to the cross-over design of clinical trials, the actual incidence of myocarditis and pericarditis cannot be reliably estimated however, based on published literature presented in the Clinical Overview, the CIOMS frequency category for myocarditis and pericarditis is "very rare."[89]
g. Source = Local Reactions, by Maximum Severity, Within 7 Days After First Study Vaccination - Cohort 2 – Safety Population (Study C4591031 SSD, Cutoff date: 11 March 2022)

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Table A-11. Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency Within Each System Organ Class: Individuals >55 years old Who Received a Booster (Dose 4) of Bivalent BNT162b2 (15 µg) + BNT162b2 OMI BA.1 (15 µg) in Study C4591031 Substudy E (SSE) – Expanded Cohort – Safety Population (16 May 2022 Data Cut-off Date)[64]

System Organ Class	ADR Term	Frequency n/N (%)
Blood and lymphatic system disorders	Lymphadenopathy	1/305 (0.3%)[a]
Immune system disorders	Anaphylaxis[b]	
	Hypersensitivity reactions	
	Rash[b,c]	
	Pruritus[b,c]	
	Urticaria[b,c]	
	Angioedema[b,c]	
Metabolism and nutrition disorders	Decreased appetite[c]	
Nervous system disorders	Headache	101/301 (33.6%)[d]
	Lethargy[c]	
Cardiac disorders	Myocarditis[b]	N/A[e]
	Pericarditis[b]	N/A[e]
Gastrointestinal disorders	Diarrhea[b]	27/301 (9.0%)[d]
	Vomiting[b]	5/301 (1.7%)[d]
	Nausea	1/305 (0.3%)[a]
Skin and subcutaneous tissue disorders	Hyperhidrosis[c]	
	Night sweats[c]	
Musculoskeletal and connective tissue disorders	Myalgia (muscle pain)	67/301 (22.3%)[d]
	Arthralgia (joint pain) (new)	34/301 (11.3%)[d]
	Pain in extremity (arm)[b,c]	
General disorders and administration site conditions	Injection site pain	175/301 (58.1%)[f]
	Fatigue	148/301 (49.2%)[d]
	Chills	39/301 (13.0%)[d]
	Injection site redness	21/301 (7.0%)[f]
	Injection site swelling	20/301 (6.6%)[f]
	Pyrexia	15/301 (5.0%)[d]
	Malaise	1/305 (0.3%)[a]
	Asthenia[c]	

a. Source: Number (%) of Participants Reporting at Least 1 Adverse Event From the Study Vaccination Through 1 Month After the Study Vaccination, by System Organ Class and Preferred Term — Expanded Cohort — Participants >55 Years of Age — Safety Population (Study C4591031 SSE, Cutoff date: 16May2022)
b. These adverse reactions were identified in the post-authorization period.
c. At the time of the data cut-off date, the following reactions were not reported in the safety population in Study C4591031 SSE: rash, pruritus, urticaria, angioedema, decreased appetite, lethargy, hyperhidrosis, night sweats, pain in extremity and asthenia but are still considered adverse reactions.
d. Source = Systemic Events, by Maximum Severity, Within 7 Days After the Study Vaccination – Expanded Cohort – Participants >55 Years of Age – Safety Population (Study C4591031 SSE, Cutoff date: 16May2022)
e. Due to the cross-over design of clinical trials, the actual incidence of myocarditis and pericarditis cannot be reliably estimated however, based on published literature presented in the Clinical Overview, the CIOMS frequency category for myocarditis and pericarditis is "very rare."[89]
f. Source = Local Reactions, by Maximum Severity, Within 7 Days After the Study Vaccination – Expanded Cohort – Participants >55 Years of Age – Safety Population (Study C4591031 SSE, Cutoff date: 16May2022)

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Table A-12. Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency Within Each System Organ Class: Individuals 5 Through <12 Years of Age Who Received a Booster Dose (Dose 3) of BNT162b2 (22 March 2022 Data Cut-off Date)[*,64,84]

System Organ Class	ADR Term	Frequency n/N (%)
Blood and lymphatic system disorders	Lymphadenopathy[a]	10/401 (2.5%)[b]
Immune system disorders	Anaphylaxis[e]	Not known
	Hypersensitivity reactions	
	Rash[e]	1/401 (0.2%)[b]
	Urticaria[e,f]	
	Pruritus[e,f]	
	Angioedema[e,f]	
Metabolism and nutrition disorders	Decreased appetite[f]	
Nervous system disorders	Headache	126/371 (34.0%)[c]
	Lethargy[f]	
Cardiac Disorders	Myocarditis[e,f]	N/A[g]
	Pericarditis[e,f]	N/A[g]
Gastrointestinal disorders	Diarrhea[e]	18/371 (4.9%)[c]
	Vomiting[e]	9/371 (2.4%)[c]
	Nausea[f]	
Skin and subcutaneous tissue disorders	Hyperhidrosis[f]	
	Night sweats[f]	
Musculoskeletal and connective tissue disorders	Myalgia (muscle pain)	68/371 (18.3%)[c]
	Arthralgia (joint pain) (new)	25/371 (6.7%)[c]
	Pain in extremity (arm)[e,f]	
General disorders and administration site conditions	Injection site pain	274/371 (73.9%)[d]
	Fatigue	169/371 (45.6%)[c]
	Injection site swelling	61/371 (16.4%)[d]
	Injection site redness	58/371 (15.6%)[d]
	Chills	39/371 (10.5%)[c]
	Pyrexia	25/371 (6.7%)[c]
	Malaise[f]	
	Asthenia[f]	

* Booster dose (Dose 3) of BNT162b2 10 µg was administered to participants 5 through <12 years of age in Study C4591007.

a. A higher frequency of lymphadenopathy was observed in participants 5 through <12 years of age in Study C4591007 (2.5% vs. 0.9%) receiving a booster dose compared to participants receiving 2 doses. The frequency of lymphadenopathy was calculated as follows: lymphadenopathy (n = 8), lymph node palpable (n = 1), axillary mass (n = 1) (8+1+1 = 10/401 = 2.5%).

b. Source: Number (%) of Participants Reporting at Least 1 Adverse Event From Dose 3 to 1 Month After Dose 3, by System Organ Class and Preferred Term – Phase 2/3 – Participants Who Received Dose 3 of BNT162b2 – 5 to <12 Years of Age – Safety Population (Study C4591007, Cut-off date: 22 March 2022).

c. Source = Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Phase 2/3 – Participants Who Received Dose 3 of BNT162b2 – 5 to <12 Years of Age – Safety Population (Study C4591007, Cut-off date: 22 March 2022).

d. Source = Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Phase 2/3 – Participants Who Received Dose 3 of BNT162b2 – 5 to <12 Years of Age – Safety Population (Study C4591007, Cut-off date: 22 March 2022).

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

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f. At the time of the data cut-off date, the following reactions were not reported in participants 5 through <12 Years of Age in Study C4591007 after Dose 3: urticaria, pruritus, angioedema, decreased appetite, lethargy, myocarditis, pericarditis, nausea, night sweats, hyperhidrosis, pain in extremity (arm), malaise, asthenia but are still considered adverse reactions.

g. Due to the cross-over design of clinical trials, the actual incidence of myocarditis and pericarditis cannot be reliably estimated however, based on published literature presented in the Clinical Overview, the CIOMS frequency category for myocarditis and pericarditis is "very rare."[89]

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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

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)[64]

System Organ Class	Very Common ≥1/10 (≥10%)	Common ≥1/100 to <1/10 (≥1% to <10%)	Uncommon ≥1/1,000 to <1/100 (≥0.1% to <1%)	Rare ≥1/10,000 to <1/1,000 (≥0.01% to <0.1%)	Very Rare <1/10,000 (<0.01%)	Frequency not known (cannot be estimated from the available data)
Blood and lymphatic system disorders			Lymphadenopathy			
Immune system disorders			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			
Cardiac disorders					Myocarditis[a]; Pericarditis[a]	
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			

* CIOMS frequency categories are based on clinical trial C4591001 crude incidence and was reported to only one significant figure.

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.

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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)[64]

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

* CIOMS frequency categories are based on clinical trial C4591001 crude incidence and was reported to only one significant figure.

a. These adverse reactions were identified in the post-authorization period. The following events were not reported in the 12 through 15 years of age group in Study C4591001: angioedema, pruritus, malaise, lethargy, asthenia, decreased appetite, hyperhidrosis, and night sweats but are still considered adverse reactions for this age group.

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

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Table B-3. ADRs by System Organ Class and CIOMS Frequency Category* Listed in Order of Decreasing Medical Seriousness Within Each Frequency Category and System Organ Class: Individuals 5 Through <12 Years of Age (06 September 2021 Data Cut-off Date)[64]

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

* CIOMS frequency categories are based on clinical trial C4591007 crude incidence and was reported to only one significant figure.

a. These adverse reactions were identified in the post-authorization period. At the time of the data cut-off date, the following reactions were not reported in participants 5 through <12 years of age in Study C4591007: angioedema, lethargy, myocarditis, pericarditis, asthenia, hyperhidrosis, and night sweats but are still considered adverse reactions for this age group.

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

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Table B-4. ADRs by System Organ Class and CIOMS Frequency Category* Listed in order of Decreasing Medical Seriousness Within Each Frequency Category and System Organ Class: Individuals 2 to <5 Years of Age (29 April 2022 Data Cut-off Date)[64]

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

* CIOMS frequency categories are based on clinical trial C4591007 crude incidence and was reported to only one significant figure.

a. These adverse reactions were identified in the post-authorization period. At the time of the data cut-off date, the following reactions were not reported in participants 2 to <5 Years of Age in Study C4591007: pruritus, angioedema, lethargy, myocarditis, pericarditis, hyperhidrosis, night sweats, and malaise but are still considered adverse reactions for this age group.

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

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Table B-5. ADRs by System Organ Class and CIOMS Frequency Category* Listed in Order of Decreasing Medical Seriousness Within Each Frequency Category and System Organ Class: Individuals 6 Months to <2 Years of Age (29 April 2022 Data Cut-off Date)[64]

System Organ Class	Very Common ≥1/10 (≥10%)	Common ≥1/100 to <1/10 (≥1% to <10%)	Uncommon ≥1/1,000 to <1/100 (≥0.1% to <1%)	Rare ≥1/10,000 to <1/1,000 (≥0.01% to <0.1%)	Very Rare <1/10,000 (<0.01%)	Frequency not known (cannot be estimated from the available data)
Blood and lymphatic system disorders			Lymphadenopathy			
Immune system disorders		Rash[a,b]	Urticaria[a,b]			Anaphylaxis[a]
Metabolism and nutrition disorders	Decreased appetite					
Psychiatric disorders	Irritability					
Nervous system disorders			Headache Lethargy			
Gastrointestinal disorders		Vomiting[a,] Diarrhea[a]				
General disorders and administration site conditions	Injection site tenderness; Injection site redness; Pyrexia	Injection site swelling	Fatigue; Chills			

* CIOMS frequency categories are based on clinical trial C4591007 crude incidence and was reported to only one significant figure.

a. These adverse reactions were identified in the post-authorization period. At the time of the data cut-off date, the following reactions were not reported in participants 6 months to <2 Years of Age in Study C4591007: pruritus, angioedema, myocarditis, pericarditis, nausea, hyperhidrosis, night sweats, myalgia, arthralgia, pain in extremity, malaise, and asthenia but are still considered adverse reactions for this age group.

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

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Table B-6. ADRs by SOC and CIOMS Frequency Category* Listed in Order of Decreasing Medical Seriousness Within Each Frequency Category and SOC: BNT162b2-Experienced Individuals (18 to 55 Years of Age) Who Were Rerandomized to Receive 1 Booster (Dose 3) of BNT162b2 (30 µg) – Booster Safety Population (17 June 2021 Data Cut-off Date)†,[64]

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

* CIOMS frequency categories are based on clinical trial C4591001 crude incidence and was reported to only one significant figure.

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

a. These adverse reactions were identified in the post-authorization period. The following events were not reported in the booster safety population in Study C4591001: angioedema, pruritus, urticaria, malaise, lethargy, asthenia, hyperhidrosis, and night sweats but are still considered adverse reactions for this age group.

b. The following event is categorized as a hypersensitivity reaction: rash.

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Table B-7. Non-reactogenicity* ADRs by System Organ Class and CIOMS Frequency Category† Listed in Order of Decreasing Medical Seriousness Within Each Frequency Category and System Organ Class: Study C4591031 Substudy A (SSA), Individuals ≥16 Years of Age who Received 1 Booster (Dose 3) of BNT162b2 (30 µg) in Study C4591031 SSA (5 October 2021 Data Cut-off Date)[64]

System Organ Class	Very Common ≥1/10 (≥10%)	Common ≥1/100 to <1/10 (≥1% to <10%)	Uncommon ≥1/1,000 to <1/100 (≥0.1% to <1%)	Rare ≥1/10,000 to <1/1,000 (≥0.01% to <0.1%)	Very Rare <1/10,000 (<0.01%)	Frequency not known (cannot be estimated from the available data)
Blood and lymphatic system disorders		Lymphadenopathy				
Immune system disorders			Pruritus[a,b]; Rash[a,b]	Urticaria[a,b]		Anaphylaxis[a]
Metabolism and nutrition disorders			Decreased appetite			
Nervous system disorders			Lethargy			
Cardiac disorders					Myocarditis[a]; Pericarditis[a]	
Gastrointestinal disorders			Nausea			
Skin and subcutaneous tissue disorders			Hyperhidrosis; Night sweats			
Musculoskeletal and connective tissue disorders		Pain in extremity (arm)[a]				
General disorders and administration site conditions			Asthenia; Malaise			

* Please see Table A-6 and Table B-6 for the frequencies and CIOMS Frequency Categories for the following reactogenicity adverse reactions that were reported in the booster safety population of Study C4591001: headache, diarrhea, vomiting, myalgia (muscle pain), arthralgia (joint pain) (new), injection site pain, fatigue, chills, pyrexia, injection site swelling, injection site redness.

† CIOMS frequency categories are based on clinical trial C4591031 crude incidence and was reported to only one significant figure.

Please see Table B-6 for the CIOMS Frequency Categories for the following reactogenicity adverse reactions that were reported in the booster safety population of Study C4591001: headache, diarrhea, vomiting, myalgia (muscle pain), arthralgia (joint pain) (new), injection site pain, fatigue, chills, pyrexia, injection site swelling, injection site redness.

The preferred term pyrexia is a cluster term also covering 'body temperature increased'.

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

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

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Table B-8. ADRs by System Organ Class and CIOMS Frequency Category* Listed in order of Decreasing Medical Seriousness Within Each Frequency Category and System Organ Class: Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency Within Each System Organ Class: Individuals 18 to 55 years old Who Received a Booster (Dose 4) of BNT162b2 30 µg in Study C4591031 Substudy D (SSD) — Safety Population (11 March 2022 Data Cut-off Date)[64]

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

* CIOMS frequency categories are based on clinical trial C4591031 SSD crude incidence and was reported to only one significant figure.

a. These adverse reactions were identified in the post-authorization period. At the time of the data cut-off date, the following reactions were not reported in the safety population in Study C4591031 SSD: rash, pruritus, urticaria, angioedema, decreased appetite, lethargy, nausea, hyperhidrosis, night sweats, pain in extremity, malaise, and asthenia but are still considered adverse reactions.

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Table B-9. ADRs by System Organ Class and CIOMS Frequency Category* Listed in Order of Decreasing Medical Seriousness Within Each Frequency Category and System Organ Class: Individuals >55 years old Who Received a Booster (Dose 4) of BNT162b2 30 µg in Study C4591031 Substudy E (SSE) – Expanded Cohort – Safety Population (16 May 2022 Data Cut-off Date)[64]

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

* CIOMS frequency categories are based on clinical trial C4591031 SSE crude incidence and was reported to only one significant figure.

a. These adverse reactions were identified in the post-authorization period. At the time of the data cut-off date, the following reactions were not reported in the safety population in Study C4591031 SSE: rash, pruritus, urticaria, angioedema, decreased appetite, lethargy, hyperhidrosis, night sweats, malaise and asthenia but are still considered adverse reactions.

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Table B-10. ADRs by System Organ Class and CIOMS Frequency Category* Listed in Order of Decreasing Medical Seriousness Within Each Frequency Category and System Organ Class: Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency Within Each System Organ Class: Individuals 18 to 55 Years Old Who Received a Booster (Dose 4) of Monovalent BNT162b2 OMI BA.1 (30 µg) in Study C4591031 Substudy D (SSD) — Safety Population (11 March 2022 Data Cut-off Date)[64]

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

* CIOMS frequency categories are based on clinical trial C4591031 SSD crude incidence and was reported to only one significant figure.

a. These adverse reactions were identified in the post-authorization period. At the time of the data cut-off date, the following reactions were not reported in the safety population in Study C4591031 SSD: rash, pruritus, urticaria, angioedema, decreased appetite, lethargy, nausea, hyperhidrosis, pain in extremity, malaise, and asthenia but are still considered adverse reactions.

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Table B-11. ADRs by System Organ Class and CIOMS Frequency Category* Listed in order of Decreasing Medical Seriousness Within Each Frequency Category and System Organ Class: Individuals >55 years old Who Received a Booster (Dose 4) of Bivalent BNT162b2 (15 µg) + BNT162b2 OMI BA.1 (15 µg) in Study C4591031 Substudy E (SSE) – Expanded Cohort – Safety Population (16 May 2022 Data Cut-off Date)[64]

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

* CIOMS frequency categories are based on clinical trial C4591031 SSE crude incidence and was reported to only one significant figure.
a. These adverse reactions were identified in the post-authorization period. At the time of the data cut-off date, the following reactions were not reported in the safety population in Study C4591031 SSE: rash, pruritus, urticaria, angioedema, decreased appetite, lethargy, hyperhidrosis, night sweats, pain in extremity and asthenia but are still considered adverse reactions.

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Table B-12. ADRs by System Organ Class and CIOMS Frequency Category* Listed in Order of Decreasing Medical Seriousness Within Each Frequency Category and System Organ Class: Individuals 5 Through <12 Years of Age Who Received Dose 3 (22 March 2022 Data Cut-off Date)[†,64,84]

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

* CIOMS frequency categories are based on clinical trial C4591007 crude incidence and was reported to only one significant figure.

† Dose 3 (a booster dose) of BNT162b2 10 µg was administered to participants 5 through <12 years of age in Study C4591007.

a. These adverse reactions were identified in the post-authorization period. At the time of the data cut-off date, the following reactions were not reported in participants 5 through <12 years of age in Study C4591007 after Dose 3: urticaria, pruritus, angioedema, decreased appetite, lethargy, myocarditis, pericarditis, nausea, night sweats, hyperhidrosis, pain in extremity (arm), malaise, and asthenia but are still considered adverse reactions in this age group.

b. The following event is categorized as a hypersensitivity reaction: rash.

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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.

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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

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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 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.

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