

## 1. NAME OF THE MEDICINAL PRODUCT

COMIRNATY, COVID-19 mRNA Vaccine (nucleoside modified), 30 micrograms/dose Dispersion for Injection

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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).

	<b>COMIRNATY (For 12 Years of Age and Older) (Vials with Grey Cap)</b>
<b>Age</b>	12 years of age and older
<b>Pharmaceutical form</b>	Dispersion for injection
<b>Strength</b>	30 micrograms/dose
<b>Cap color</b>	Grey
<b>Dilution</b>	Do not dilute
<b>Presentation</b>	Tris/Sucrose

COMIRNATY 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 SARS-CoV-2.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Dispersion for injection

The vaccine is a white to off-white frozen dispersion (pH: 6.9 - 7.9).

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

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

### 4.2 Posology and method of administration

#### Posology

COMIRNATY (For 12 Years of Age and Older) (Vials with Grey Cap) is administered intramuscularly as a primary series of 2 doses (0.3 mL each). It is recommended to administer the second dose at least 21 days (preferably 3 weeks) after the first dose (see sections 4.4 and 5.1).

### Booster dose

A booster dose of COMIRNATY may be administered intramuscularly after the second dose. The decision when and for whom to implement a booster dose of COMIRNATY should be made based on available vaccine safety and effectiveness data, in accordance with official recommendations.

Doses of COMIRNATY, COVID-19 mRNA Vaccine (nucleoside modified), 30 micrograms/dose Dispersion for Injection and COMIRNATY Concentrate for Dispersion for Injection (30 micrograms/dose) are considered interchangeable.

COMIRNATY (For 12 Years of Age and Older) (Vials with Grey Cap) intended for individuals ages 12 years and older cannot be used for individuals age 5 years to <12 years.

### Interchangeability

The interchangeability of COMIRNATY 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 COMIRNATY should receive a second dose of COMIRNATY 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.

For further information on efficacy, see section 5.1.

### Paediatric population

The safety and efficacy of COMIRNATY in paediatric participants aged less than 5 years have not yet been established. Limited data are available.

### Elderly population

No dosage adjustment is required in elderly individuals  $\geq 65$  years of age. The safety of a booster dose of COMIRNATY 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 COMIRNATY 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.

### Method of administration

COMIRNATY should be administered intramuscularly (see section 6.6). The preferred site is the deltoid muscle of the upper arm.

Do not inject the vaccine intravascularly, subcutaneously or intradermally.

Vials of COMIRNATY (For 12 Years of Age and Older) (Vials with Grey Cap) contain 6 doses of 0.3 mL of vaccine.

Low dead-volume syringes and/or needles can be used to extract 6 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial. Irrespective of the type of syringe and needle:

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

- Do not pool excess vaccine from multiple vials.

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

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

For instructions regarding thawing, handling, dilution, dose preparation of vaccine before administration, and disposal of the vaccine, see section 6.6.

### **4.3 Contraindications**

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

### **4.4 Special warnings and precautions for use**

#### Traceability

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

#### General recommendations

##### *Hypersensitivity and anaphylaxis*

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

Close observation for at least 30 minutes is recommended following vaccination. A second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose of COMIRNATY.

##### *Myocarditis and pericarditis*

Postmarketing data demonstrate increased risks of myocarditis and pericarditis, particularly within 7 days following the second dose. The observed risk is higher among males under 40 years of age than among females and older males. The observed risk is highest in males 12 through 17 years of age. Although some cases required intensive care support, available data from short-term follow-up suggest that most individuals have had resolution of symptoms with conservative management. Information is not yet available about potential long-term sequelae. Vaccine recipients should be advised to avoid strenuous physical activity for two weeks after vaccination. They should be advised to seek medical attention promptly if they develop chest pain, shortness of breath or abnormal heartbeats.

##### *Stress-related responses*

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.

##### *Concurrent illness*

Vaccination should be postponed in individuals suffering from acute severe febrile illness or acute infection.

#### *Thrombocytopenia and coagulation disorders*

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

#### *Immunocompromised individuals*

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

#### *Duration of protection*

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

#### *Limitations of vaccine effectiveness*

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

### **4.5 Interaction with other medicinal products and other forms of interaction**

No interaction studies have been performed.

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

### **4.6 Fertility, pregnancy and lactation**

#### Pregnancy

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

#### Breast-feeding

It is unknown whether COMIRNATY is excreted in human milk.

#### Fertility

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

### **4.7 Effects on ability to drive and use machines**

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

## 4.8 Undesirable effects

### Summary of safety profile

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

The overall safety profile of COMIRNATY in adolescents 12 through 15 years of age was similar to that seen in participants 16 years of age and older.

Additionally, 306 existing Phase 3 participants at least 18 through 55 years of age received a booster dose of COMIRNATY 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.

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 COMIRNATY at least 6 months after the second dose. The overall safety profile for the booster dose was similar to that seen after 2 doses.

#### *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 COMIRNATY and a total of 22,021 participants 16 years of age or older received placebo (including 138 and 145 adolescents 16 and 17 years of age in the vaccine and placebo groups, respectively). A total of 20,519 participants 16 years of age or older received 2 doses of COMIRNATY.

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

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

The safety profile in 545 participants 16 years of age and older receiving COMIRNATY, that were seropositive for SARS-CoV-2 at baseline, was similar to that seen in the general population.

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

#### *Adolescents 12 through 15 years of age – after 2 doses*

In an analysis of long-term safety follow-up in Study 2, based on data up to the cut-off date of 13 March 2021, 2,260 adolescents (1,131 COMIRNATY and 1,129 placebo) were 12 through 15 years of age. Of these, 1,559 adolescents (786 COMIRNATY and 773 placebo) have been followed for  $\geq 4$  months after the second dose. 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%).

In adolescents 12 through 15 years of age, psychiatric-related serious adverse events were numerically higher in the vaccine group, 4 recipients (3 [0.3%] with depression and 1 [0.1%] with suicidal ideation) and none in the placebo group. The events in the vaccine group were confounded by prior medical history as all 4 participants had concurrent psychiatric illness including depression prior to vaccination. Currently available information is insufficient to determine a causal relationship with the vaccine.

#### *Children 5 through <12 years of age – after 2 doses*

In an analysis of Study 3 Phase 2/3, 2,268 participants (1,518 COMIRNATY 10 micrograms; 750 placebo) were 5 through <12 years of age. Of these, 2,158 (95.1%) (1,444 COMIRNATY 10 micrograms and 714 placebo) participants have been followed for at least 2 months after the second dose. An analysis of Study 3 Phase 2/3 adverse event data also included another 2,379 participants (1,591 COMIRNATY 10 micrograms and 788 placebo), of whom 71.2% had a follow-up period for at least 2 weeks after Dose 2 up to the cut-off date of 8 October 2021. 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*

A subset from Study 2 Phase 2/3 participants of 306 adults at least 18 through 55 years of age who completed the primary COMIRNATY 2-dose course, received a booster dose of COMIRNATY 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 COMIRNATY (5,081 participants), or placebo (5,044 participants) at least 6 months after the second dose of COMIRNATY. 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).

#### Tabulated list of adverse reactions from clinical studies and post-authorisation experience

Adverse reactions observed during clinical studies are listed below according to the following frequency categories:

Very common ( $\geq 1/10$ ),

Common ( $\geq 1/100$  to  $< 1/10$ ),

Uncommon ( $\geq 1/1,000$  to  $< 1/100$ ),

Rare ( $\geq 1/10,000$  to  $< 1/1,000$ ),

Very rare ( $< 1/10,000$ ),

Not known (cannot be estimated from the available data).

**Table 1: Adverse reactions from COMIRNATY clinical trials and post-authorisation experience in individuals 12 years of age and older\***

<b>System Organ Class</b>	<b>Very common (≥ 1/10)</b>	<b>Common (≥ 1/100 to &lt; 1/10)</b>	<b>Uncommon (≥ 1/1,000 to &lt; 1/100)</b>	<b>Rare (≥ 1/10,000 to &lt; 1/1,000)</b>	<b>Not known (cannot be estimated from the available data)</b>
Blood and lymphatic system disorders			Lymphadenopathy <sup>a</sup>		
Immune system disorders			Hypersensitivity reactions (e.g., rash, pruritus, urticaria, <sup>b</sup> angioedema <sup>b</sup> )		Anaphylaxis
Metabolism and nutrition disorder			Decreased appetite		
Psychiatric disorders			Insomnia		
Nervous system disorders	Headache		Lethargy	Acute peripheral facial paralysis <sup>c</sup>	
Cardiac disorders					Myocarditis; <sup>d</sup> Pericarditis <sup>d</sup>
Gastrointestinal disorders	Diarrhoea <sup>d</sup>	Nausea; Vomiting <sup>d</sup>			
Skin and subcutaneous tissue disorder			Hyperhidrosis; Night sweats		
Musculoskeletal and connective tissue disorders	Arthralgia; Myalgia		Pain in extremity <sup>e</sup>		
General disorders and administration site conditions	Injection site pain; Fatigue; Chills; Pyrexia; <sup>f</sup> Injection site swelling	Injection site redness	Asthenia; Malaise; Injection site pruritus		

<b>System Organ Class</b>	<b>Very common (≥ 1/10)</b>	<b>Common (≥ 1/100 to &lt; 1/10)</b>	<b>Uncommon (≥ 1/1,000 to &lt; 1/100)</b>	<b>Rare (≥ 1/10,000 to &lt; 1/1,000)</b>	<b>Not known (cannot be estimated from the available data)</b>
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- \* CIOMS frequency categories are based on clinical trial crude incidence and was reported to only one significant figure.
- A higher frequency of lymphadenopathy (2.8% vs 0.4%) was observed in participants receiving a booster dose in Study 4 compared to participants receiving 2 doses.
  - The frequency category for urticaria and angioedema was rare.
  - Through the clinical trial safety follow-up period to 14 November 2020, acute peripheral facial paralysis (or palsy) was reported by four participants in the COVID-19 mRNA Vaccine group. Onset was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.
  - Adverse reaction determined post-authorisation.
  - Refers to vaccinated arm. 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.
  - 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.

**Table 2: Adverse reactions from COMIRNATY clinical trials and post-authorisation experience in individuals 5 years to <12 years of age (06 September 2021 data cut-off date)\***

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



<b>System Organ Class</b>	<b>Very common (≥ 1/10)</b>	<b>Common (≥ 1/100 to &lt; 1/10)</b>	<b>Uncommon (≥ 1/1,000 to &lt; 1/100)</b>	<b>Rare (≥ 1/10,000 to &lt; 1/1,000)</b>	<b>Not known (cannot be estimated from the available data)</b>
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- \* CIOMS frequency categories are based on clinical trial crude incidence and was reported to only one significant figure.
- These adverse reactions were identified in the post-authorization period. The following events were not reported in participants 5 to <12 Years of Age in Study C4591007 but were reported in individuals ≥16 years of age in Study C4591001: angioedema, lethargy, asthenia, hyperhidrosis, and night sweats.
  - The following events are categorized as hypersensitivity reactions: urticaria, pruritus, and rash.

#### Other Reporting Instructions

Vaccination providers may report all other adverse events, to the extent feasible, to Pfizer Singapore using the contact information below.

<b>Email</b>	<b>Fax number</b>	<b>Telephone number</b>
<a href="mailto:SGP.AEReporting@pfizer.com">SGP.AEReporting@pfizer.com</a>	8001012817 (local toll free)	+65 6403 8888

#### Adverse Event Reporting to HSA

Healthcare professionals are required to report any suspected serious adverse events observed with the use of COMIRNATY to HSA as soon as possible. All fatal and life-threatening events are to be reported as soon as possible, within 24 hours. Please report the adverse events to the Vigilance and Compliance Branch at Tel: 6866 1111, Fax: 6478 9069, or report online at <https://www.hsa.gov.sg/adverse-events>.

#### **4.9 Overdose**

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

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

### **5. PHARMACOLOGICAL PROPERTIES**

#### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: vaccines, other viral vaccines, ATC code: J07BX03

#### Mechanism of action

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

## Efficacy

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

### *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 were randomised equally and were to receive 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. Participants are planned to be followed for up to 24 months after Dose 2, for assessments of safety and efficacy against COVID-19. In the clinical study, participants were required to observe a minimum interval of 14 days before and after administration of an influenza vaccine in order to receive either placebo or COVID-19 mRNA Vaccine. In the clinical study, participants were required to observe a minimum interval of 60 days before or after receipt of blood/plasma products or immunoglobulins within through conclusion of the study in order to receive either placebo or COVID-19 mRNA Vaccine.

The population for the analysis of the primary efficacy endpoint included, 36,621 participants 12 years of age and older (18,242 in the COVID-19 mRNA Vaccine group and 18,379 in the placebo group) who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose. In addition, 134 participants were between the ages of 16 through 17 years of age (66 in the COVID-19 mRNA Vaccine group and 68 in the placebo group) and 1,616 participants 75 years of age and older (804 in the COVID-19 mRNA Vaccine group and 812 in the placebo group).

**Table 3: Demographics (Population for the Primary Efficacy Endpoint)<sup>a</sup>**

	<b>COVID-19 mRNA Vaccine (N=18,242) n (%)</b>	<b>Placebo (N=18,379) n (%)</b>
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		
$\geq 12$ through 15 years <sup>b</sup>	46 (0.3)	42 (0.2)
$\geq 16$ through 17 years	66 (0.4)	68 (0.4)
$\geq 16$ through 64 years	14,216 (77.9)	14,299 (77.8)
$\geq 65$ through 74 years	3176 (17.4)	3226 (17.6)
$\geq 75$ 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 <sup>c</sup>	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 <sup>d</sup>		
Yes	8432 (46.2)	8450 (46.0)
No	9810 (53.8)	9929 (54.0)

- All eligible randomised participants who receive all vaccination(s) as randomised 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.
- 100 participants 12 through 15 years of age with limited follow-up in the randomised population received at least one dose (49 in the vaccine group and 51 in the placebo group). Some of these participants were included in the efficacy evaluation depending on the population analysed. They contributed to exposure information but with no confirmed COVID-19 cases, and did not affect efficacy conclusions.
- Includes multiracial and not reported.
- Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease
  - Chronic lung disease (e.g., emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, and cystic fibrosis) or moderate to severe asthma
  - Significant cardiac disease (e.g., heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension)
  - Obesity (body mass index  $\geq 30$  kg/m<sup>2</sup>)
  - 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 in total 2,214 person-years for the COVID-19 mRNA Vaccine and in total 2,222 person-years in the placebo group.

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

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 prior to 7 days after Dose 2 – evaluable efficacy (7 days) population**

First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection*			
Subgroup	COVID-19 mRNA Vaccine N <sup>a</sup> = 18,198 Cases n <sup>1b</sup> Surveillance time <sup>c</sup> (n <sup>2d</sup> )	Placebo N <sup>a</sup> = 18,325 Cases n <sup>1b</sup> Surveillance time <sup>c</sup> (n <sup>2d</sup> )	Vaccine efficacy % (95% CI) <sup>e</sup>
All participants	8	162	95.0 (90.0, 97.9)

<b>First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection*</b>			
<b>Subgroup</b>	<b>COVID-19 mRNA Vaccine N<sup>a</sup> = 18,198 Cases n1<sup>b</sup> Surveillance time<sup>c</sup> (n2<sup>d</sup>)</b>	<b>Placebo N<sup>a</sup> = 18,325 Cases n1<sup>b</sup> Surveillance time<sup>c</sup> (n2<sup>d</sup>)</b>	<b>Vaccine efficacy % (95% CI)<sup>e</sup></b>
	2.214 (17,411)	2.222 (17,511)	
16 through 64 years	7 1.706 (13,549)	143 1.710 (13,618)	95.1 (89.6, 98.1)
65 years and older	1 0.508 (3848)	19 0.511 (3880)	94.7 (66.7, 99.9)
65 through 74 years	1 0.406 (3074)	14 0.406 (3095)	92.9 (53.1, 99.8)
75 years and older	0 0.102 (774)	5 0.106 (785)	100.0 (-13.1, 100.0)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 [\*Case definition: (at least 1 of) fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhoea or vomiting.]

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

- N = Number of participants in the specified group.
- n1 = Number of participants meeting the endpoint definition.
- 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.
- n2 = Number of participants at risk for the endpoint.
- Confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time. CI not adjusted for multiplicity.

Efficacy of COVID-19 mRNA Vaccine in preventing first COVID-19 occurrence from 7 days after Dose 2 compared to placebo was 94.6% (95% confidence interval of 89.6% to 97.6%) in participants 16 years of age and older with or without evidence of prior infection with SARS-CoV-2.

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

Updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up through March 13, 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 5.

**Table 5: 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**

<b>First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection*</b>			
<b>Subgroup</b>	<b>COVID-19 mRNA Vaccine</b>	<b>Placebo N<sup>a</sup>=21,096 Cases</b>	<b>Vaccine Efficacy %</b>

	<b>N<sup>a</sup>=20,998</b> <b>Cases</b> <b>n1<sup>b</sup></b> <b>Surveillance Time<sup>c</sup></b> <b>(n2<sup>d</sup>)</b>	<b>n1<sup>b</sup></b> <b>Surveillance Time<sup>c</sup></b> <b>(n2<sup>d</sup>)</b>	<b>(95% CI<sup>e</sup>)</b>
All participants <sup>f</sup>	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)
<b>First COVID-19 occurrence from 7 days after Dose 2 in participants with or without* evidence of prior SARS-CoV-2 infection</b>			
<b>Subgroup</b>	<b>COVID-19 mRNA Vaccine N<sup>a</sup>=22,166 Cases n1<sup>b</sup></b> <b>Surveillance Time<sup>c</sup></b> <b>(n2<sup>d</sup>)</b>	<b>Placebo N<sup>a</sup>=22,320 Cases n1<sup>b</sup></b> <b>Surveillance Time<sup>c</sup></b> <b>(n2<sup>d</sup>)</b>	<b>Vaccine Efficacy % (95% CI<sup>e</sup>)</b>
All participants <sup>f</sup>	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; diarrhoea; 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 COVID-19 mRNA Vaccine 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 6 and Table 7.

**Table 6: 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**

<b>Subgroup</b>	<b>COVID-19 mRNA Vaccine N<sup>a</sup>=20,998 Cases n<sup>1</sup><sup>b</sup> Surveillance Time<sup>c</sup> (n<sup>2</sup><sup>d</sup>)</b>	<b>Placebo N<sup>a</sup>=21,096 Cases n<sup>1</sup><sup>b</sup> Surveillance Time<sup>c</sup> (n<sup>2</sup><sup>d</sup>)</b>	<b>Vaccine Efficacy % (95% CI)<sup>e</sup></b>
<b>Sex</b>			
Male	42 3.246 (10,637)	399 3.047 (10,433)	90.1 (86.4, 93.0)
Female	35 3.001 (10,075)	451 2.956 (10,280)	92.4 (89.2, 94.7)
<b>Ethnicity</b>			
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)
<b>Race</b>			
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 <sup>f</sup>	6 0.494 (1789)	55 0.451 (1720)	90.0 (76.9, 96.5)
<b>Country</b>			
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)

<b>Subgroup</b>	<b>COVID-19 mRNA Vaccine</b> <b>N<sup>a</sup>=20,998</b> <b>Cases</b> <b>n1<sup>b</sup></b> <b>Surveillance Time<sup>c</sup></b> <b>(n2<sup>d</sup>)</b>	<b>Placebo</b> <b>N<sup>a</sup>=21,096</b> <b>Cases</b> <b>n1<sup>b</sup></b> <b>Surveillance Time<sup>c</sup></b> <b>(n2<sup>d</sup>)</b>	<b>Vaccine Efficacy %</b> <b>(95% CI)<sup>e</sup></b>
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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; diarrhoea; vomiting).

Included confirmed cases in participants 12 through 15 years of age: 0 in the COVID-19 mRNA Vaccine 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.

- N = Number of participants in the specified group.
- n1 = Number of participants meeting the endpoint definition.
- 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.
- n2 = Number of participants at risk for the endpoint.
- Two-sided confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
- All others = American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported race categories.

**Table 7: 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**

<b>Subgroup</b>	<b>COVID-19 mRNA Vaccine</b> <b>N<sup>a</sup>=22,166</b> <b>Cases</b> <b>n1<sup>b</sup></b> <b>Surveillance Time<sup>c</sup></b> <b>(n2<sup>d</sup>)</b>	<b>Placebo</b> <b>N<sup>a</sup>=22,320</b> <b>Cases</b> <b>n1<sup>b</sup></b> <b>Surveillance Time<sup>c</sup></b> <b>(n2<sup>d</sup>)</b>	<b>Vaccine Efficacy %</b> <b>(95% CI)<sup>e</sup></b>
<b>Sex</b>			
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)
<b>Ethnicity</b>			
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)
<b>Race</b>			
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)

<b>Subgroup</b>	<b>COVID-19 mRNA Vaccine N<sup>a</sup>=22,166 Cases n1<sup>b</sup> Surveillance Time<sup>c</sup> (n2<sup>d</sup>)</b>	<b>Placebo N<sup>a</sup>=22,320 Cases n1<sup>b</sup> Surveillance Time<sup>c</sup> (n2<sup>d</sup>)</b>	<b>Vaccine Efficacy % (95% CI)<sup>e</sup></b>
All others <sup>f</sup>	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; diarrhoea; vomiting).

Included confirmed cases in participants 12 through 15 years of age: 0 in the COVID-19 mRNA Vaccine 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 updated subgroup analyses of vaccine efficacy by risk status in participants are presented in Table 8 and Table 9.



**Table 8: 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**

<b>Subgroup</b>	<b>COVID-19 mRNA Vaccine N<sup>a</sup>=20,998 Cases n<sup>1</sup><sup>b</sup> Surveillance Time<sup>c</sup> (n<sup>2</sup><sup>d</sup>)</b>	<b>Placebo N<sup>a</sup>=21,096 Cases n<sup>1</sup><sup>b</sup> Surveillance Time<sup>c</sup> (n<sup>2</sup><sup>d</sup>)</b>	<b>Vaccine Efficacy % (95% CI)<sup>e</sup></b>
First COVID-19 occurrence from 7 days after Dose 2 <sup>f</sup>	77 6.247 (20,712)	850 6.003 (20,713)	91.3 (89.0, 93.2)
At risk <sup>g</sup>			
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)
<b>Age group (years) and risk status</b>			
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)
<b>Obese<sup>h</sup></b>			
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)
<b>Age group (years) and obesity status</b>			
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; diarrhoea; 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.

<b>Subgroup</b>	<b>COVID-19 mRNA Vaccine N<sup>a</sup>=20,998 Cases n1<sup>b</sup> Surveillance Time<sup>c</sup> (n2<sup>d</sup>)</b>	<b>Placebo N<sup>a</sup>=21,096 Cases n1<sup>b</sup> Surveillance Time<sup>c</sup> (n2<sup>d</sup>)</b>	<b>Vaccine Efficacy % (95% CI)<sup>e</sup></b>
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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 for surveillance time.
- f. Included confirmed cases in participants 12 through 15 years of age: 0 in the COVID-19 mRNA Vaccine group; 16 in the placebo group.
- g. At risk is defined as having at least 1 of the Charlson Comorbidity Index (CMI) category or obesity (BMI  $\geq 30$  kg/m<sup>2</sup> or BMI  $\geq 95^{\text{th}}$  percentile [12 through 15 Years of age]).
- h. Obese is defined as BMI  $\geq 30$  kg/m<sup>2</sup>. For 12 through 15 years age group, obesity is defined as a BMI at or above the 95<sup>th</sup> percentile. Refer to the CDC growth charts at [https://www.cdc.gov/growthcharts/html\\_charts/bmiagerev.htm](https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm).

**Table 9: 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**

<b>Subgroup</b>	<b>COVID-19 mRNA Vaccine N<sup>a</sup>=22,166 Cases n1<sup>b</sup> Surveillance Time<sup>c</sup> (n2<sup>d</sup>)</b>	<b>Placebo N<sup>a</sup>=22,320 Cases n1<sup>b</sup> Surveillance Time<sup>c</sup> (n2<sup>d</sup>)</b>	<b>Vaccine Efficacy % (95% CI)<sup>e</sup></b>
First COVID-19 occurrence from 7 days after Dose 2 <sup>f</sup>	81 6.509 (21,642)	873 6.274 (21,689)	91.1 (88.8, 93.0)
At risk <sup>g</sup>			
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 <sup>h</sup>			
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)

<b>Subgroup</b>	<b>COVID-19 mRNA Vaccine N<sup>a</sup>=22,166 Cases n1<sup>b</sup> Surveillance Time<sup>c</sup> (n2<sup>d</sup>)</b>	<b>Placebo N<sup>a</sup>=22,320 Cases n1<sup>b</sup> Surveillance Time<sup>c</sup> (n2<sup>d</sup>)</b>	<b>Vaccine Efficacy % (95% CI)<sup>e</sup></b>
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; diarrhoea; 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.

- N = Number of participants in the specified group.
- n1 = Number of participants meeting the endpoint definition.
- 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.
- n2 = Number of participants at risk for the endpoint.
- Two-sided confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.
- Included confirmed cases in participants 12 through 15 years of age: 0 in the COVID-19 mRNA Vaccine group; 18 in the placebo group.
- At risk is defined as having at least 1 of the Charlson Comorbidity Index (CMI) category or obesity (BMI  $\geq 30$  kg/m<sup>2</sup> or BMI  $\geq 95^{\text{th}}$  percentile [12 through 15 years of age]).
- Obese is defined as BMI  $\geq 30$  kg/m<sup>2</sup>. For the 12 through 15 years of age group, obesity is defined as a BMI at or above the 95<sup>th</sup> percentile. Refer to the CDC growth charts at [https://www.cdc.gov/growthcharts/html\\_charts/bmiagerev.htm](https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm).

### Efficacy Against Severe COVID-19 – After 2 Doses

Updated efficacy analyses of secondary efficacy endpoints supported benefit of the COVID-19 mRNA Vaccine in preventing severe COVID-19. Vaccine efficacy against severe COVID-19 is presented only for participants with or without prior SARS-CoV-2 infection (Table 10) 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 COVID-19 mRNA Vaccine and placebo groups.

**Table 10: 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**

<b>Vaccine Efficacy – First Severe COVID-19 Occurrence Based on FDA Definition</b>			
	<b>COVID-19 mRNA Vaccine Cases n1<sup>a</sup></b> <b>Surveillance Time (n2<sup>b</sup>)</b>	<b>Placebo Cases n1<sup>a</sup></b> <b>Surveillance Time (n2<sup>b</sup>)</b>	<b>Vaccine Efficacy % (95% CI)<sup>c</sup></b>
After Dose 1 <sup>d</sup>	1 8.439 <sup>e</sup> (22,505)	30 8.288 <sup>e</sup> (22,435)	96.7 (80.3, 99.9)
7 days after Dose 2 <sup>f</sup>	1 6.522 <sup>g</sup> (21,649)	21 6.404 <sup>g</sup> (21,730)	95.3 (70.9, 99.9)
<b>Vaccine Efficacy – First Severe COVID-19 Occurrence Based on CDC Definition</b>			
	<b>COVID-19 mRNA Vaccine Cases n1<sup>a</sup></b> <b>Surveillance Time (n2<sup>b</sup>)</b>	<b>Placebo Cases n1<sup>a</sup></b> <b>Surveillance Time (n2<sup>b</sup>)</b>	<b>Vaccine Efficacy % (95% CI)<sup>c</sup></b>
After Dose 1 <sup>d</sup>	1 8.427 <sup>e</sup> (22,473)	45 8.269 <sup>e</sup> (22,394)	97.8 (87.2, 99.9)
7 days after Dose 2 <sup>f</sup>	0 6.514 <sup>g</sup> (21,620)	32 6.391 <sup>g</sup> (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; diarrhoea; 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:

- Clinical signs at rest indicative of severe systemic illness (respiratory rate  $\geq 30$  breaths per minute, heart rate  $\geq 125$  beats per minute, saturation of oxygen  $\leq 93\%$  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:

- Hospitalisation;
- 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 randomised participants who received at least 1 dose of study intervention.
- e. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.
- f. Efficacy assessed based on the evaluable efficacy (7 Days) population that included all eligible randomised participants who receive all dose(s) of study intervention as randomised within the predefined window, have no other important protocol deviations as determined by the clinician.
- 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 through 15 years of age – after 2 doses*

In an analysis of Study 2 in adolescents 12 through 15 years of age without evidence of prior infection, there were no cases in 1005 participants who received the vaccine and 16 cases out of 978 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 75.3, 100.0). In participants with or without evidence of prior infection there were 0 cases in the 1119 who received vaccine and 18 cases in 1110 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 78.1, 100.0).

In Study 2, an analysis of SARS-CoV-2 neutralising titres 1 month after Dose 2 was conducted in a randomly selected subset of participants who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2, comparing the response in adolescents 12 through 15 years of age (n = 190) to participants 16 through 25 years of age (n = 170).

The ratio of the geometric mean titres (GMT) in the 12 through 15 years of age group to the 16 through 25 years of age group was 1.76, with a 2-sided 95% CI of 1.47 to 2.10. Therefore, the 1.5-fold non-inferiority criterion was met as the lower bound of the 2-sided 95% CI for the geometric mean ratio [GMR] was > 0.67.

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.

The updated vaccine efficacy information in adolescents 12 through 15 years of age is presented in Table 11.

**Table 11: 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**

<b>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*</b>			
	<b>COVID-19 mRNA Vaccine N<sup>a</sup>=1057 Cases n<sup>1</sup><sup>b</sup> Surveillance Time<sup>c</sup> (n<sup>2</sup><sup>d</sup>)</b>	<b>Placebo N<sup>a</sup>=1030 Cases n<sup>1</sup><sup>b</sup> Surveillance Time<sup>c</sup> (n<sup>2</sup><sup>d</sup>)</b>	<b>Vaccine Efficacy % (95% CI<sup>e</sup>)</b>
Adolescents 12 through 15 years of age	0 0.343 (1043)	28 0.322 (1019)	100.0 (86.8, 100.0)

<b>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</b>			
	<b>COVID-19 mRNA Vaccine</b> N <sup>a</sup> =1119 Cases n <sup>1</sup> <sup>b</sup> Surveillance Time <sup>c</sup> (n <sup>2</sup> <sup>d</sup> )	<b>Placebo</b> N <sup>a</sup> =1109 Cases n <sup>1</sup> <sup>b</sup> Surveillance Time <sup>c</sup> (n <sup>2</sup> <sup>d</sup> )	<b>Vaccine Efficacy %</b> (95% CI <sup>e</sup> )
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; diarrhoea; 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.

- N = Number of participants in the specified group.
- n<sup>1</sup> = Number of participants meeting the endpoint definition.
- 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.
- n<sup>2</sup> = Number of participants at risk for the endpoint.
- 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 11 years of age without evidence of infection prior to 7 days after Dose 2. This analysis evaluated confirmed symptomatic COVID-19 cases accrued up to a data cut-off date of October 8, 2021.

Table 12 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 12: Demographics Characteristics – Participants Without Evidence of Infection Prior to 7 Days After Dose 2 – Phase 2/3 – 5 Through 11 Years of Age – Evaluable Efficacy Population**

	<b>COVID-19 mRNA Vaccine*</b> <b>10 micrograms/dose</b> (N <sup>a</sup> =1305) n <sup>b</sup> (%)	<b>Placebo</b> (N <sup>a</sup> =663) n <sup>b</sup> (%)
<b>Sex</b>		
Male	679 (52.0)	343 (51.7)
Female	626 (48.0)	320 (48.3)
<b>Age at Vaccination</b>		
Mean (SD)	8.2 (1.93)	8.1 (1.98)
Median	8.0	8.0
Min, max	(5, 11)	(5, 11)
<b>Race</b>		
White	1018 (78.0)	514 (77.5)
Black or African American	76 (5.8)	48 (7.2)

	<b>COVID-19 mRNA Vaccine* 10 micrograms/dose (N<sup>a</sup>=1305) n<sup>b</sup> (%)</b>	<b>Placebo (N<sup>a</sup>=663) n<sup>b</sup> (%)</b>
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 <sup>c</sup>	110 (8.4)	52 (7.8)
<b>Ethnicity</b>		
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%
<b>Comorbidities<sup>d</sup></b>		
Yes	262 (20.1)	133 (20.1)
No	1043 (79.9)	530 (79.9)

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

- 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 randomised participants who received all vaccination(s) as randomised within the predefined window, had no other important protocol deviations as determined by the clinician.
- n = Number of participants with the specified characteristic.
- Includes multiracial and not reported.
- 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  $\geq$ 95<sup>th</sup> percentile).

The descriptive vaccine efficacy results in children 5 through 11 years of age without evidence of prior SARS-CoV-2 infection are presented in Table 13. 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.

**Table 13: Vaccine Efficacy – First COVID-19 Occurrence From 7 days After Dose 2: Without Evidence of Infection Prior to 7 Days After Dose 2 – Phase 2/3 – Children 5 Through 11 Years of Age Evaluable Efficacy Population**

<b>First COVID-19 Occurrence From 7 days After Dose 2 in Children 5 through 11 Years of Age Without Evidence of Prior SARS-CoV-2 Infection*</b>			
	<b>COVID-19 mRNA Vaccine 10 micrograms/dose N<sup>a</sup>=1305 Cases n1<sup>b</sup> Surveillance time<sup>c</sup> (n2<sup>d</sup>)</b>	<b>Placebo N<sup>a</sup>=663 Cases n1<sup>b</sup> Surveillance time<sup>c</sup> (n2<sup>d</sup>)</b>	<b>Vaccine efficacy % (95% CI)</b>
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; diarrhoea; 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.
- N = Number of participants in the specified group.
  - n1 = Number of participants meeting the endpoint definition.
  - 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.
  - n2 = Number of participants at risk for the endpoint.

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

Study 3 is a Phase 1/2/3 study comprised of an open-label vaccine dose finding portion (Phase 1) and a multicentre, multinational, randomised, 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% neutralising titres (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 14.

**Table 14: Summary of Geometric Mean Ratio for 50% Neutralising Titre – Comparison of Children 5 Through Less Than 12 Years of Age (Study 3) to Participants 16 Through 25 Years of Age (Study 2) – Participants Without\* Evidence of Infection up to 1 Month After Dose 2 – Dose 2 Evaluable Immunogenicity Population**

		COVID-19 mRNA Vaccine		5 Through <12 Years/ 16 Through 25 Years	
		10 micrograms /Dose 5 Through <12 Years n <sup>a</sup> =264	30 micrograms /Dose 16 Through 25 Years n <sup>a</sup> =253		
Assay	Time Point <sup>b</sup>	GMT <sup>c</sup> (95% CI <sup>c</sup> )	GMT <sup>c</sup> (95% CI <sup>c</sup> )	GMR <sup>d</sup> (95% CI <sup>d</sup> )	Met Immunobridging Objective <sup>e</sup> (Y/N)
SARS-CoV-2 neutralisation assay - NT50 (titre) <sup>f</sup>	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 titre; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; NT50 = 50% neutralising titre; 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.
- 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 titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to  $0.5 \times$  LLOQ.
- d. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (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  $\geq 0.8$ .
- f. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralisation Assay. The assay uses a fluorescent reporter virus derived from the USA\_WA1/2020 strain and virus neutralisation is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralised.

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 15.

**Table 15: Difference in Percentages of Participants With Seroresponse – Participants Without\* Evidence of Infection up to 1 Month After Dose 2 – Immunobridging Subset – Phase 2/3 – Comparison of 5 Through <12 Years of Age to Study 2 Phase 2/3 16 Through 25 Years of Age – Evaluable Immunogenicity Population**

		COVID-19 mRNA Vaccine		5 Through <12 Years/ 16 Through 25 Years	
		Study 3 10 micrograms /Dose 5 Through < 12 Years N <sup>a</sup> =264	Study 2 30 micrograms /Dose 16 Through 25 Years N <sup>a</sup> =253		
Assay	Time Point <sup>b</sup>	n <sup>c</sup> (%) (95% CI <sup>d</sup> )	n <sup>c</sup> (%) (95% CI <sup>d</sup> )	Difference % <sup>e</sup> (95% CI <sup>f</sup> )	Met Immunobridging Objective <sup>g</sup> (Y/N)
SARS-CoV-2 neutralization assay - NT50 (titre) <sup>h</sup>	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% neutralising titre 50; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Seroresponse is defined as achieving a  $\geq 4$ -fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result  $\geq 4 \times$  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 neutralised.

*Immunogenicity in participants 18 years of age and older – after booster dose*

Effectiveness of a booster dose of COMIRNATY was demonstrated by evaluating non-inferiority 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 non-inferiority criteria for both GMR and difference in seroresponse rates. Seroresponse for a participant was defined as achieving a  $\geq 4$ -fold rise from baseline (before Dose 1) in NT50 (Table 16 and Table 17).

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

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

**Table 16: Summary of Geometric Mean Ratio for 50% Neutralising Titre – 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**

Assay	n <sup>a</sup>	COVID-19 mRNA Vaccine Sampling Time Point		1 Month After Booster Dose - 1 Month After Dose 2	Met Non-inferiority Objective <sup>d</sup> (Y/N)
		1 Month After Booster Dose	1 Month After Dose 2		
		GMT <sup>b</sup> (95% CI <sup>b</sup> )	GMT <sup>b</sup> (95% CI <sup>b</sup> )	GMR <sup>c</sup> (97.5% CI <sup>c</sup> )	
SARS-CoV-2 neutralisation assay - reference strain - NT50 (titre) <sup>e</sup>	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 titre; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralising titre; 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 titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to  $0.5 \times$  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. Non-inferiority 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  $\geq 0.80$ .
- e. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralisation Assay. The assay uses a fluorescent reporter virus derived from the USA\_WA1/2020 strain and virus neutralisation is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralised.

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

Assay	N <sup>a</sup>	COVID-19 mRNA Vaccine Sampling Time Point		Difference (1 Month After Booster Dose - 1 Month After Dose 2)	Met Non-inferiority Objective <sup>f</sup> (Y/N)
		1 Month After Booster Dose	1 Month After Dose 2		
		n <sup>b</sup> % (95% CI <sup>c</sup> )	n <sup>b</sup> % (95% CI <sup>c</sup> )	% <sup>d</sup> (97.5% CI <sup>e</sup> )	
SARS-CoV-2 neutralisation assay - reference strain - NT50 (titre) <sup>g</sup>	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% neutralising titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; Y/N = yes/no.

Note: Seroresponse is defined as achieving a  $\geq 4$ -fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result  $\geq 4 \times$  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. Non-inferiority 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 Microneutralisation Assay. The assay uses a fluorescent reporter virus derived from the USA\_WA1/2020 strain and virus neutralisation is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralised.

*Relative vaccine efficacy in participants 16 years of age and older – after booster dose*

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 COMIRNATY 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 18.

**Table 18: 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**

<b>First COVID-19 occurrence from 7 days after booster dose in participants without evidence of prior SARS-CoV-2 infection*</b>			
	<b>COMIRNATY N<sup>a</sup>=4695 Cases n<sup>1</sup><sup>b</sup> Surveillance Time<sup>c</sup> (n<sup>2</sup><sup>d</sup>)</b>	<b>Placebo N<sup>a</sup>=4671 Cases n<sup>1</sup><sup>b</sup> Surveillance Time<sup>c</sup> (n<sup>2</sup><sup>d</sup>)</b>	<b>Relative Vaccine Efficacy<sup>e</sup> % (95% CI<sup>f</sup>)</b>
First COVID-19 occurrence from 7 days after booster vaccination	6 0.823 (4659)	123 0.792 (4614)	95.3 (89.5, 98.3)
<b>First COVID-19 occurrence from 7 days after booster dose in participants with or without evidence of prior SARS-CoV-2 infection</b>			
	<b>COMIRNATY N<sup>a</sup>=4993 Cases n<sup>1</sup><sup>b</sup> Surveillance Time<sup>c</sup> (n<sup>2</sup><sup>d</sup>)</b>	<b>Placebo N<sup>a</sup>=4952 Cases n<sup>1</sup><sup>b</sup> Surveillance Time<sup>c</sup> (n<sup>2</sup><sup>d</sup>)</b>	<b>Relative Vaccine Efficacy<sup>e</sup> % (95% CI<sup>f</sup>)</b>
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; diarrhoea; 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.

- N = Number of participants in the specified group.
- n1 = Number of participants meeting the endpoint definition.
- 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.
- n2 = Number of participants at risk for the endpoint.
- Relative vaccine efficacy of the COMIRNATY booster group relative to the placebo group (non-booster).
- Two-sided confidence interval (CI) for relative vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.

## 5.2 Pharmacokinetic properties

Not applicable.

### 5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity and reproductive and developmental toxicity.

#### General toxicity

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

#### Genotoxicity/Carcinogenicity

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

#### Reproductive toxicity

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

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)

2 [(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)

1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)

Cholesterol

Tromethamine (Tris base)

Tris (hydroxymethyl) aminoethane hydrochloride (Tris HCl)

Sucrose

Water for injection

### 6.2 Incompatibilities

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

### 6.3 Shelf life

#### Unopened vial

12 months at -90 °C to -60 °C.

COMIRNATY (For 12 Years of Age and Older) (Vials with Grey Cap) 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.

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 °C to 30 °C for up to 24 hours, including any time at these temperatures following first puncture.

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 °C to 30 °C. 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.

### **6.4 Special precautions for storage**

COMIRNATY (For 12 Years of Age and Older) (Vials with Grey Cap) 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, minimise 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

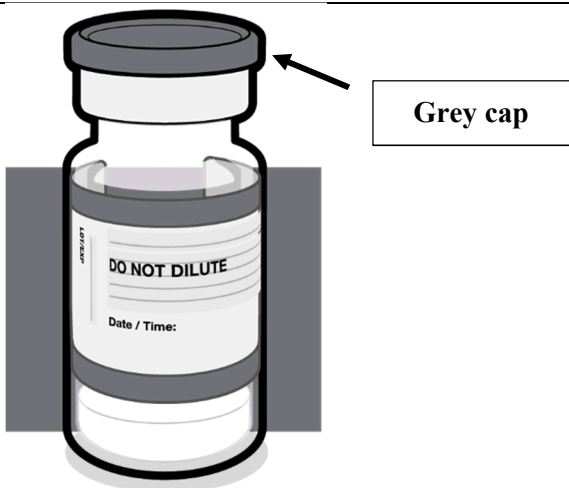
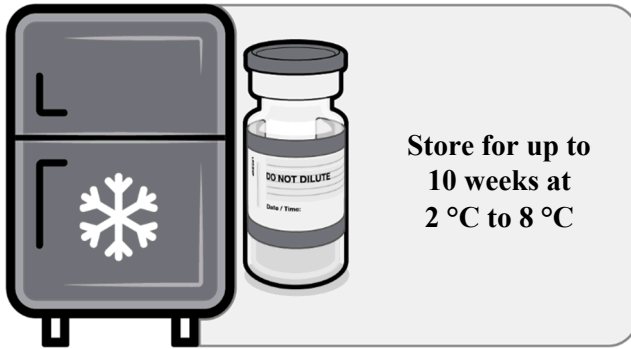
2 mL clear multidose vial (type I glass) with a stopper (synthetic bromobutyl rubber) and a flip-off plastic cap with aluminium seal, or 2 mL aluminosilicate glass vial with a stopper (bromobutyl rubber) and a flip-off plastic cap with aluminum seal.

Pack size: 10 multidose vials per carton.

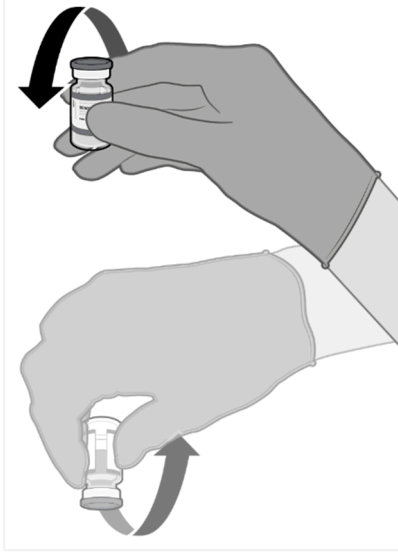
### 6.6 Special precautions for disposal and other handling

#### Handling instructions

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

<b>COMIRNATY (Do Not Dilute) (For Age 12 Years and Older)</b>	
<b>VIAL VERIFICATION</b>	
	<ul style="list-style-type: none"> <li>• Verify that the vial has a grey plastic cap. If the vial has an orange plastic cap, refer to the handling instructions for COMIRNATY (For Age 5 Years to &lt;12 Years) (Vials with Orange Cap).</li> </ul>
<b>HANDLING PRIOR TO USE</b>	
	<ul style="list-style-type: none"> <li>• 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.</li> <li>• Update the expiry date on the carton.</li> <li>• Unopened vials can be stored for up to 10 weeks at 2 °C to 8 °C; not exceeding the printed expiry date (EXP).</li> <li>• Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C for immediate use.</li> </ul>

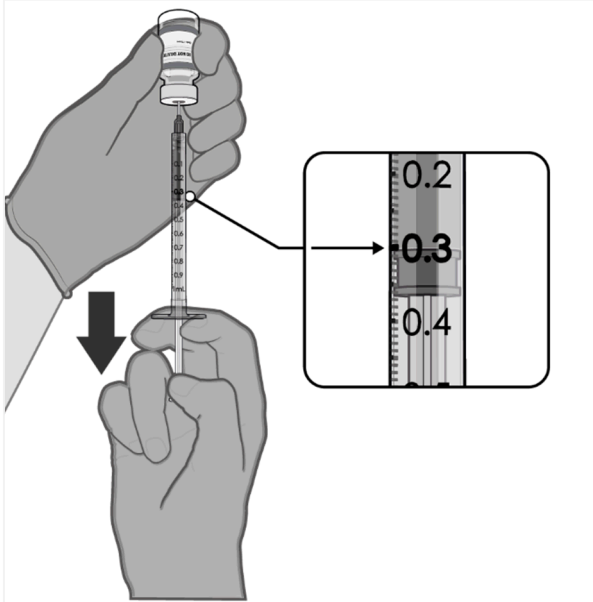
**COMIRNATY (Do Not Dilute) (For Age 12 Years and Older)**



**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 COMIRNATY**



**0.3 mL vaccine**

- Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
- Withdraw 0.3 mL of COMIRNATY.

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

If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial.

- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
- Discard any unused vaccine 12 hours after first puncture. Record the appropriate date/time on the vial.

Disposal

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




## 7. PRODUCT OWNER

BioNTech Manufacturing GmbH  
An der Goldgrube 12  
55131 Mainz  
Germany

## 8. CONTACT INFORMATION

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

Website	Telephone number
<p data-bbox="331 640 657 667"><a href="http://www.comirnatyglobal.com">www.comirnatyglobal.com</a></p> 	<p data-bbox="1007 734 1187 761">+65 6403 8888</p>

For medical information enquiries, please submit your medical information enquires at <https://pmiform.com/HCP/SG>.

Alternatively, you may send them to [MedicalInformationSingapore@pfizer.com](mailto:MedicalInformationSingapore@pfizer.com).

COM30-SIN-0322/0

Date of Last Revision: March 2022