



**FOR 6 MONTHS TO 4 YEARS OF AGE  
DILUTE BEFORE USE**

## COMIRNATY™

### 1. NAME OF THE MEDICINAL PRODUCT

Comirnaty™  
JN.1 (3 micrograms)/dose  
Concentrate for dispersion for injection  
COVID-19 mRNA Vaccine

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

This is a multidose vial with a **yellow cap** and must be diluted before use.

One vial (0.48 mL) contains **3 doses of 0.3 mL** after dilution, see sections **4.2. Posology and Method of Administration** and **6.6. Special Precautions for Disposal and Other Handling**.

One dose (0.3 mL) contains 3 micrograms of bretovameran, a COVID-19 mRNA Vaccine (nucleoside modified, embedded in lipid nanoparticles).

Bretovameran is a 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 (JN.1).

For the full list of excipients, see section **6.1. List of Excipients**.

### 3. PHARMACEUTICAL FORM

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

### 4. CLINICAL PARTICULARS

#### 4.1. Therapeutic Indications

Comirnaty JN.1 (3 micrograms)/dose concentrate for dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in infants and children aged 6 months to 4 years.

#### 4.2. Posology and Method of Administration

##### Posology

*Infants and children 6 months to 4 years of age without history of completion of a COVID-19 primary course or prior SARS-CoV-2 infection*

Comirnaty JN.1 (3 micrograms)/dose with **yellow cap** is administered intramuscularly after dilution as a primary course of 3 doses (**0.3 mL each**). It is recommended to administer the second dose 3 weeks after the first dose followed by a third dose administered at least 8 weeks after the second dose (see sections **4.4. Special Warnings and Precautions for Use** and **5.1. Pharmacodynamic Properties**).

If a child turns 5 years old between their doses in the primary course, he/she should complete the primary

course at the same 3 micrograms dose level.

***Infants and children 6 months to 4 years of age with history of completion of a COVID-19 primary course or prior SARS CoV-2 infection***

Comirnaty JN.1 (3 micrograms)/dose with **yellow cap** is administered intramuscularly after dilution as a single dose of **0.3 mL** for infants and children 6 months to 4 years of age.

For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty JN.1 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

***Severely immunocompromised aged 6 months to 4 years***

Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations (see section **4.4. Special Warnings and Precautions for Use**).

***Interchangeability***

The primary course may consist of either Comirnaty, Comirnaty Original/Omicron BA.4-5, Comirnaty Omicron XBB.1.5 or Comirnaty JN.1 (or a combination) but not exceeding the total number of doses required as primary course. The primary course should only be administered once.

The interchangeability of Comirnaty with COVID-19 vaccines from other manufacturers has not been established.

***Paediatric population***

There are paediatric formulations available for children 5 to 11 years of age. For details, please refer to the product leaflet for other formulations.

The safety and efficacy of the vaccine in infants aged less than 6 months have not yet been established.

**Method of administration**

Comirnaty JN.1 (3 micrograms)/dose concentrate for dispersion for injection should be administered intramuscularly after dilution (see section **6.6. Special Precautions for Disposal and Other Handling**).

After dilution, vials with a **yellow cap** of Comirnaty JN.1 contain **3 doses of 0.3 mL** of vaccine. Standard syringes and needles can be used to extract 3 doses 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.

In infants from 6 to less than 12 months of age, the recommended injection site is the anterolateral aspect of the thigh. In individuals 1 year of age and older, the recommended injection site is the anterolateral aspect of the thigh or the deltoid muscle.

Do not inject the vaccine intravascularly, subcutaneously or intradermally.

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

For precautions to be taken before administering the vaccine, see section **4.4. Special Warnings and Precautions for Use**.

For instructions regarding thawing, dilution, handling and disposal of the vaccine, see section **6.6. Special Precautions for Disposal and Other Handling**.

### **4.3. Contraindications**

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

### **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.

#### **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. No further dose of the vaccine should be given to those who have experienced anaphylaxis after a prior dose of Comirnaty.

#### **Myocarditis and pericarditis**

There is an increased risk of myocarditis and pericarditis following vaccination with Comirnaty. These conditions can develop within just a few days after vaccination, and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males (see section **4.8. Undesirable Effects**). Available data indicate that most cases recover. Some cases required intensive care support and fatal cases have been observed.

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees (including parents or caregivers) should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination.

Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

#### **Anxiety-related reactions**

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions (e.g., dizziness, palpitations, increases in heart rate, alterations in blood pressure, paraesthesia, hypoaesthesia and sweating) may occur in association with the vaccination process itself. Stress-related reactions are temporary and resolve on their own. Individuals should be advised to bring symptoms to the attention of the vaccination provider for evaluation. It is important that precautions are in place to avoid injury from fainting.

#### **Concurrent illness**

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

#### **Thrombocytopenia and coagulation disorders**

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

#### **Immunocompromised individuals**

The efficacy and safety of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of Comirnaty JN.1 may be lower in immunocompromised 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 JN.1 may not protect all vaccine recipients. Individuals may not be fully protected until 7 days after their vaccination.

#### **4.5. Interaction with Other Medicinal Products and Other Forms of Interaction**

No interaction studies have been performed.

Concomitant administration of Comirnaty JN.1 with other vaccines has not been studied.

#### **4.6. Fertility, Pregnancy and Lactation**

Comirnaty JN.1 (3 micrograms)/dose concentrate for dispersion for injection is not intended for individuals older than 5 years of age.

For details for use in individuals older than 5 years of age, please refer to the product leaflet for those formulations.

#### **4.7. Effects on Ability to Drive and Use Machines**

Comirnaty JN.1 has no or negligible influence on the ability to drive, cycle, and use machines. However, some of the effects mentioned under section **4.8. Undesirable Effects** may temporarily affect the ability to drive, cycle, or use machines.

#### **4.8. Undesirable Effects**

##### **Summary of safety profile**

The safety of Comirnaty JN.1 is inferred from safety data of the prior Comirnaty vaccines.

##### *Comirnaty*

##### *Infants 6 to 23 months of age – after 3 doses*

In an analysis of Study 3 (Phase 2/3), 2176 infants (1458 initially approved Comirnaty 3 mcg and 718 placebo) were 6 to 23 months of age. Based on data in the blinded placebo-controlled follow-up period up to the cut-off date of 28 February 2023, 720 infants 6 to 23 months of age who received a 3-dose primary course (483 Comirnaty 3 mcg and 237 placebo) have been followed for a median of 1.7 months after the third dose.

The most frequent adverse reactions in infants 6 to 23 months of age that received any primary course dose included irritability (> 60%), drowsiness (> 40%), decreased appetite (> 30%), tenderness at the injection site (> 20%), injection site redness and fever (> 10%).

##### *Children 2 to 4 years of age – after 3 doses*

In an analysis of Study 3 (Phase 2/3), 3541 children (2368 Comirnaty 3 mcg and 1173 placebo) were 2 to 4 years of age. Based on data in the blinded placebo-controlled follow-up period up to the cut-off date of 28 February 2023, 1268 children 2 to 4 years of age who received a 3-dose primary course (863 Comirnaty 3 mcg and 405 placebo) have been followed a median of 2.2 months after the third dose.

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

##### *Children 5 to 11 years of age (i.e., 5 to less than 12 years of age) – after 2 doses*

In Study 3, a total of 3109 children 5 to 11 years of age received at least 1 dose of Comirnaty 10 mcg and a total of 1538 children 5 to 11 years of age received placebo. At the time of the analysis of Study 3 Phase 2/3 with data up to the cut-off date of 20 May 2022, 2206 (1481 Comirnaty 10 mcg and 725 placebo) children have been followed for  $\geq 4$  months after the second dose in the placebo-controlled blinded follow-up period. The safety evaluation in Study 3 is ongoing.

The overall safety profile of Comirnaty in participants 5 to 11 years of age was similar to that seen in participants 16 years of age and older. The most frequent adverse reactions in children 5 to 11 years of age that received 2 doses were injection site pain (> 80%), fatigue (> 50%), headache (> 30%), injection

site redness and swelling ( $\geq 20\%$ ), myalgia, chills, and diarrhoea ( $> 10\%$ ).

*Children 5 to 11 years of age (i.e., 5 to less than 12 years of age) – after booster dose*

In a subset from Study 3, a total of 2408 children 5 to 11 years of age received a booster dose of Comirnaty 10 mcg at least 5 months (range of 5.3 to 19.4 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 28 February 2023 (median follow-up time of 6.4 months).

The overall safety profile for the booster dose was similar to that seen after the primary course. The most frequent adverse reactions in children 5 to 11 years of age after the booster dose were injection site pain ( $> 60\%$ ), fatigue ( $> 30\%$ ), headache ( $> 20\%$ ), myalgia, chills, injection site redness and swelling ( $> 10\%$ ).

*Adolescents 12 to 15 years of age – after 2 doses*

In an analysis of long-term safety follow-up in Study 2, 2260 adolescents (1131 Comirnaty and 1129 placebo) were 12 to 15 years of age. Of these, 1559 adolescents (786 Comirnaty and 773 placebo) have been followed for  $\geq 4$  months after the second dose.

The overall safety profile of Comirnaty in adolescents 12 to 15 years of age was similar to that seen in participants 16 years of age and older. The most frequent adverse reactions in adolescents 12 to 15 years of age that received 2 doses were injection site pain ( $> 90\%$ ), fatigue and headache ( $> 70\%$ ), myalgia and chills ( $> 40\%$ ), arthralgia and pyrexia ( $> 20\%$ ).

*Participants 16 years of age and older – after 2 doses*

In Study 2, a total of 22026 participants 16 years of age or older received at least 1 dose of Comirnaty 30 mcg and a total of 22021 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 20519 participants 16 years of age or older received 2 doses of Comirnaty.

At the time of the analysis of Study 2 with a data cut-off of 13 March 2021 for the placebo-controlled blinded follow-up period up to the participants' unblinding dates, a total of 25651 (58.2%) participants (13031 Comirnaty and 12620 placebo) 16 years of age and older were followed up for  $\geq 4$  months after the second dose. This included a total of 15111 (7704 Comirnaty and 7407 placebo) participants 16 to 55 years of age and a total of 10540 (5327 Comirnaty and 5213 placebo) participants 56 years of age 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 ( $> 40\%$ ), 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.

*Participants 12 years of age and older – after booster dose*

A subset from Study 2 Phase 2/3 participants of 306 adults 18 to 55 years of age who completed the original 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. Overall, participants who received a booster dose, had a median follow-up time of 8.3 months (range 1.1 to 8.5 months) and 301 participants had been followed for  $\geq 6$  months after the booster dose to the cut-off date (22 November 2021).

The overall safety profile for the booster dose was similar to that seen after 2 doses. The most frequent adverse reactions in participants 18 to 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 (5081 participants), or placebo (5044 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 2.8 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). Of these, 1281 participants (895 Comirnaty and 386 placebo) have been followed for  $\geq 4$  months after the booster dose of Comirnaty. No new adverse reactions of Comirnaty were identified.

A subset from Study 2 Phase 2/3 participants of 825 adolescents 12 to 15 years of age who completed the original Comirnaty 2-dose course, received a booster dose of Comirnaty approximately 11.2 months (range of 6.3 to 20.1 months) after receiving Dose 2. Overall, participants who received a booster dose, had a median follow-up time of 9.5 months (range 1.5 to 10.7 months) based on data up to the cut-off date (3 November 2022). No new adverse reactions of Comirnaty were identified.

### ***Booster dose following primary vaccination with another authorised COVID-19 vaccine***

In 5 independent studies on the use of a Comirnaty booster dose in individuals who had completed primary vaccination with another authorised COVID-19 vaccine (heterologous booster dose), no new safety issues were identified.

### ***Omicron-adapted Comirnaty***

#### *Infants 6 to 23 months of age – after the booster (fourth dose)*

In a subset from Study 6 (Phase 3), 39 participants 6 to 23 months of age who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (1.5/1.5 mcg) 2.1 to 8.6 months after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 had a median follow-up time of at least 1.7 months.

The overall safety profile for the Comirnaty Original/Omicron BA.4-5 booster (fourth dose) was similar to that seen after 3 doses. The most frequent adverse reaction in participants 6 to 23 months of age was irritability ( $> 20\%$ ), decreased appetite ( $> 10\%$ ), and drowsiness ( $> 10\%$ ).

#### *Children 2 to 4 years of age – after the booster (fourth dose)*

In a subset from Study 6 (Phase 3), 124 participants 2 to 4 years of age who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (1.5/1.5 mcg) 2.2 to 8.6 months after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 had a median follow-up time of at least 1.8 months.

The overall safety profile for the Comirnaty Original/Omicron BA.4-5 booster (fourth dose) was similar to that seen after 3 doses. The most frequent adverse reactions in participants 2 to 4 years of age were injection site pain ( $> 30\%$ ) and fatigue ( $> 20\%$ ).

#### *Children 5 to 11 years of age (i.e., 5 to less than 12 years of age) – after the booster (fourth dose)*

In a subset from Study 6 (Phase 3), 113 participants 5 to 11 years of age who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (5/5 mcg) 2.6 to 8.5 months after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 had a median follow-up time of at least 1.6 months.

The overall safety profile for the Comirnaty Original/Omicron BA.4-5 booster (fourth dose) was similar to that seen after 3 doses. The most frequent adverse reactions in participants 5 to 11 years of age were injection site pain ( $> 60\%$ ), fatigue ( $> 40\%$ ), headache ( $> 20\%$ ), and muscle pain ( $> 10\%$ ).

#### *Participants 12 years of age and older – after a booster dose of Comirnaty Original/Omicron BA.4-5 (fourth dose)*

In a subset from Study 5 (Phase 2/3), 107 participants 12 to 17 years of age, 313 participants 18 to 55 years of age and 306 participants 56 years of age and older who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (15/15 micrograms) 5.4 to 16.9 months after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 had a median follow-up time of at least 1.5 months.

The overall safety profile for the Comirnaty Original/Omicron BA.4-5 booster (fourth dose) was similar to that seen after 3 doses. The most frequent adverse reactions in participants 12 years of age and older were injection site pain (> 60%), fatigue (> 50%), headache (> 40%), muscle pain (> 20%), chills (> 10%), and joint pain (> 10%).

**Tabulated list of adverse reactions from clinical studies of Comirnaty and Comirnaty Original/Omicron BA.4-5 and post-authorisation experience of Comirnaty in individuals 6 months of age and older**

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 ( $\geq 1/1000$  to  $< 1/100$ ),
- Rare ( $\geq 1/10000$  to  $< 1/1000$ ),
- Very rare ( $< 1/10000$ ),
- Not known (cannot be estimated from the available data).

**Table 1. Adverse reactions from Comirnaty and Comirnaty Original/Omicron BA.4-5 clinical trials and Comirnaty post-authorisation experience in individuals 6 months of age and older**

System Organ Class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Common	Lymphadenopathy <sup>a</sup>
Immune system disorders	Uncommon	Hypersensitivity reactions (e.g., rash <sup>i</sup> , pruritus, urticaria, angioedema <sup>b</sup> )
	Not known	Anaphylaxis
Metabolism and nutrition disorders	Uncommon	Decreased appetite <sup>j</sup>
Psychiatric disorders	Very common	Irritability <sup>k</sup>
	Uncommon	Insomnia
Nervous system disorders	Very common	Headache; Drowsiness <sup>k</sup>
	Uncommon	Dizziness <sup>d</sup> ; Lethargy
	Rare	Acute peripheral facial paralysis <sup>c</sup>
	Not known	Paraesthesia <sup>d</sup> ; Hypoaesthesia <sup>d</sup>
Cardiac disorders	Very rare	Myocarditis <sup>d</sup> ; Pericarditis <sup>d</sup>
Gastrointestinal disorders	Very common	Diarrhoea <sup>d</sup>
	Common	Nausea; Vomiting <sup>d</sup>
Skin and subcutaneous tissue disorder	Uncommon	Hyperhidrosis; Night sweats
	Not known	Erythema multiforme <sup>d</sup>
Musculoskeletal and connective tissue disorders	Very common	Arthralgia; Myalgia
	Uncommon	Pain in extremity <sup>e</sup>
Reproductive system and breast disorders	Not known	Heavy menstrual bleeding <sup>l</sup>
General disorders and administration site conditions	Very common	Injection site pain; Injection site tenderness <sup>k</sup> ; Fatigue; Chills; Pyrexia <sup>f</sup> ; Injection site swelling
	Common	Injection site redness <sup>h</sup>
	Uncommon	Asthenia; Malaise; Injection site pruritus
	Not known	Extensive swelling of vaccinated limb <sup>d</sup> ; Facial swelling <sup>g</sup>

a. In participants 5 years of age and older, a higher frequency of lymphadenopathy was reported after a booster ( $\leq 2.8\%$ ) dose than after primary ( $\leq 0.9\%$ ) doses of the vaccine.

b. The frequency category for angioedema was rare.

c. 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.

d. Adverse reaction determined post-authorisation.

e. Refers to vaccinated arm.

f. A higher frequency of pyrexia was observed after the second dose compared to the first dose.

g. Facial swelling in vaccine recipients with a history of injection of dermatological fillers has been reported in the post-marketing phase.

h. Injection site redness occurred at a higher frequency (very common) in participants 6 months to 11 years of age.

i. The frequency category for rash was common in participants 6 to 23 months of age.

j. The frequency category for decreased appetite was very common in participants 6 to 23 months of age.

k. Irritability, injection site tenderness, and drowsiness pertain to participants 6 to 23 months of age.

l. Most cases appeared to be non-serious and temporary in nature.

## **Description of selected adverse reactions**

### ***Myocarditis and pericarditis***

The increased risk of myocarditis after vaccination with Comirnaty is highest in younger males (see section **4.4. Special Warnings and Precautions for Use**).

Two large European pharmacoepidemiological studies have estimated the excess risk in younger males following the second dose of Comirnaty. One study showed that in a period of 7 days after the second dose there were about 0.265 (95% CI 0.255 - 0.275) extra cases of myocarditis in 12-29 year-old males per 10000 compared to unexposed persons. In another study, in a period of 28 days after the second dose there were 0.56 (95% CI 0.37 - 0.74) extra cases of myocarditis in 16-24 year-old males per 10000 compared to unexposed persons.

Limited data indicate that the risk of myocarditis and pericarditis after vaccination with Comirnaty in children aged 5 to 11 years seems lower than in ages 12 to 17 years.

### **Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

### **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 reactivity 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**

Pharmaco-therapeutic group: vaccines, viral vaccines, ATC code: J07BN01

#### **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**

##### ***Omicron-adapted Comirnaty***

*Immunogenicity in infants and children 6 months to 4 years of age – after the booster (fourth dose)*



In an analysis of a subset from Study 6, 60 participants 6 months to 4 years of age received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (1.5/1.5 mcg) after receiving 3 prior doses of Comirnaty 3 micrograms dose concentrate for dispersion. Results include immunogenicity data from a comparator subset of participants 6 months to 4 years of age in Study 3 who received 3 doses of Comirnaty 3 micrograms dose concentrate for dispersion.

At 1 month after a booster dose (fourth dose), a booster dose with Comirnaty Original/Omicron BA.4-5 (1.5/1.5 mcg) elicited higher Omicron BA.4-5 specific neutralizing titres (regardless of baseline SARS-CoV-2 status) compared with the titres in the comparator group who received 3 doses of Comirnaty 3 micrograms dose concentrate for dispersion. Comirnaty Original/Omicron BA.4-5 (1.5/1.5 mcg) also elicited similar reference strain-specific titres compared with the titres in the comparator group.

The vaccine immunogenicity results after a booster dose in participants 6 months to 4 years of age are presented in **Table 2**.

**Table 2: Geometric mean titres – Study 6 subset – participants with or without evidence of infection – 6 months though 4 years of age – evaluable immunogenicity population**

SARS-CoV-2 neutralization assay	Age group	Sampling time point <sup>a</sup>	Vaccine group (as assigned/randomized)			
			Study 6 Comirnaty Original/Omicron BA.4-5 1.5/1.5 mcg Dose 4 and 1 month after Dose 4		Study 3 Comirnaty 3 mcg Dose 3 and 1 month after Dose 3	
			n <sup>b</sup>	GMT <sup>c</sup> (95% CI <sup>c</sup> )	n <sup>b</sup>	GMT <sup>c</sup> (95% CI <sup>c</sup> )
Omicron BA.4-5 - NT50 (titre) <sup>d</sup>	6 months through 4 years	Pre-vaccination	54	192.5 (120.4, 307.8)	54	70.5 (51.1, 97.2)
		1 month	58	1695.2 (1151.8, 2494.9)	54	607.9 (431.1, 857.2)
Reference strain - NT50 (titre) <sup>d</sup>	6 months through 4 years	Pre-vaccination	57	2678.1 (1913.0, 3749.2)	53	776.8 (536.4, 1125.0)
		1 month	58	9733.0 (7708.2, 12289.6)	53	9057.3 (7223.4, 11356.8)

Abbreviations: CI = confidence interval; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- 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.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).

*Immunogenicity in children 5 to 11 years of age (i.e., 5 to less than 12 years of age) – after the booster (fourth dose)*

In an analysis of a subset from Study 6, 103 participants 5 to 11 years of age who had previously received a 2-dose primary series and booster dose with Comirnaty received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5. Results include immunogenicity data from a comparator subset of participants 5 to 11 years of age in Study 3 who received 3 doses of Comirnaty. In participants 5 to 11 years of age who received a fourth dose of Comirnaty Original/Omicron BA.4-5 and participants 5 to 11 years of age who received a third dose of Comirnaty, 57.3% and 58.4% were positive for SARS-CoV-2 at baseline, respectively.

The immune response 1 month after a booster dose (fourth dose), Comirnaty Original/Omicron BA.4-5 elicited generally similar Omicron BA.4/BA.5-specific neutralizing titres compared with the titres in the

comparator group who received 3 doses of Comirnaty. Comirnaty Original/Omicron BA.4-5 also elicited similar reference strain-specific titres compared with the titres in the comparator group.

The vaccine immunogenicity results after a booster dose in participants 5 to 11 years of age are presented in **Table 3**.

**Table 3: Study 6 – Geometric mean ratio and Geometric mean titres – participants with or without evidence of infection – 5 to 11 years of age – evaluable immunogenicity population**

SARS-CoV-2 neutralization assay	Sampling time point <sup>a</sup>	Vaccine group (as assigned/randomized)				
		Study 6 Comirnaty (Original/Omicron BA.4/BA.5) 10 mcg Dose 4 and 1 month after Dose 4		Study 3 Comirnaty 10 mcg Dose 3 and 1 month after Dose 3		Study 6 Comirnaty (Original/Omicron BA.4/BA.5)/Comirnaty 10 mcg
		n <sup>b</sup>	GMT <sup>c</sup> (95% CI <sup>e</sup> )	n <sup>b</sup>	GMT <sup>c</sup> (95% CI <sup>e</sup> )	GMR <sup>d</sup> (95% CI <sup>d</sup> )
Omicron BA.4-5 - NT50 (titre) <sup>e</sup>	Pre-vaccination	102	488.3 (361.9, 658.8)	112	248.3 (187.2, 329.5)	-
	1 month	102	2189.9 (1742.8, 2751.7)	113	1393.6 (1175.8, 1651.7)	1.12 (0.92, 1.37)
Reference strain - NT50 (titre) <sup>e</sup>	Pre-vaccination	102	2904.0 (2372.6, 3554.5)	113	1323.1 (1055.7, 1658.2)	-
	1 month	102	8245.9 (7108.9, 9564.9)	113	7235.1 (6331.5, 8267.8)	-

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; LS = least square; N-binding = SARS-CoV-2 nucleoprotein-binding; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- 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.
- GMRs and 2-sided CIs were calculated by exponentiating the difference of LS Means for the assay and the corresponding CIs based on analysis of log-transformed assay results using a linear regression model with baseline log-transformed neutralizing titres, postbaseline infection status, and vaccine group as covariates.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).

*Immunogenicity in participants 12 years of age and older – after the booster (fourth dose)*

In an analysis of a subset from Study 5, 105 participants 12 to 17 years of age, 297 participants 18 to 55 years of age, and 286 participants 56 years of age and older who had previously received a 2-dose primary series and booster dose with Comirnaty received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5. In participants 12 through 17 years of age, 18 through 55 years of age, and 56 years of age and older, 75.2%, 71.7% and 61.5% were positive for SARS-CoV-2 at baseline, respectively.

Analyses of 50% neutralizing antibody titres (NT50) against Omicron BA.4-5 and against reference strain among participants 56 years of age and older who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 in Study 5 compared to a subset of participants from Study 4 who received a booster (fourth dose) of Comirnaty demonstrated superiority of Comirnaty Original/Omicron BA.4-5 to Comirnaty based on geometric mean ratio (GMR) and noninferiority based on difference in seroresponse rates with respect to anti-Omicron BA.4-5 response, and noninferiority of anti-reference strain immune response based on GMR (**Table 4**).

Analyses of NT50 against Omicron BA.4/BA.5 among participants 18 through 55 years of age compared to participants 56 years of age and older who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 in Study 5 demonstrated noninferiority of anti-Omicron BA.4-5 response

among participants 18 through 55 years of age compared to participants 56 years of age and older for both GMR and difference in seroresponse rates (**Table 4**).

The study also assessed the level of NT50 of the anti-Omicron BA.4-5 SARS-CoV-2 and reference strains pre-vaccination and 1 month after vaccination in participants who received a booster (fourth dose) (**Table 5**).

**Table 4: SARS-CoV-2 GMTs (NT50) and difference in percentages of participants with seroresponse at 1 month after vaccination course – Comirnaty Original/Omicron BA.4-5 from Study 5 and Comirnaty from subset of Study 4 – participants with or without evidence of SARS-CoV-2 infection – evaluable immunogenicity population**

SARS-CoV-2 GMTs (NT50) at 1 month after vaccination course								
SARS-CoV-2 neutralization assay	Study 5 Comirnaty Original/Omicron BA.4-5				Subset of Study 4 Comirnaty		Age group comparison	Vaccine group comparison
	18 through 55 years of age		56 years of age and older		56 years of age and older		Comirnaty Original/Omicron BA.4-5 18 through 55 years of age/≥ 56 years of age	≥ 56 years of age Comirnaty Original/Omicron BA.4-5 /Comirnaty
	n <sup>a</sup>	GMT <sup>c</sup> (95% CI <sup>c</sup> )	n <sup>a</sup>	GMT <sup>b</sup> (95% CI <sup>b</sup> )	n <sup>a</sup>	GMT <sup>b</sup> (95% CI <sup>b</sup> )	GMR <sup>c</sup> (95% CI <sup>c</sup> )	GMR <sup>c</sup> (95% CI <sup>c</sup> )
Omicron BA.4-5 - NT50 (titre) <sup>d</sup>	297	4455.9 (3851.7, 5154.8)	284	4158.1 (3554.8, 4863.8)	282	938.9 (802.3, 1098.8)	0.98 (0.83, 1.16) <sup>e</sup>	2.91 (2.45, 3.44) <sup>f</sup>
Reference Strain – NT50 (titre) <sup>d</sup>	-	-	286	16250.1 (14499.2, 18212.4)	289	10415.5 (9366.7, 11581.8)	-	1.38 (1.22, 1.56) <sup>g</sup>
Difference in percentages of participants with seroresponse at 1 month after vaccination course								
SARS-CoV-2 neutralization assay	Comirnaty Original/Omicron BA.4-5				Subset of Study 4 Comirnaty		Age group comparison	Vaccine group comparison
	18 through 55 years of age		56 years of age and older		56 years of age and older		Comirnaty Original/Omicron BA.4-5 18 through 55 years of age/≥ 56	≥ 56 years of age Comirnaty Original/Omicron BA.4-5 /Comirnaty
	N <sup>h</sup>	n <sup>i</sup> (%) (95% CI <sup>k</sup> )	N <sup>h</sup>	n <sup>i</sup> (%) (95% CI <sup>k</sup> )	N <sup>h</sup>	n <sup>i</sup> (%) (95% CI <sup>k</sup> )	Difference <sup>k</sup> (95% CI <sup>l</sup> )	Difference <sup>k</sup> (95% CI <sup>l</sup> )
Omicron BA.4-5 - NT50 (titre) <sup>d</sup>	294	180 (61.2) (55.4, 66.8)	282	188 (66.7) (60.8, 72.1)	273	127 (46.5) (40.5, 52.6)	-3.03 (-9.68, 3.63) <sup>m</sup>	26.77 (19.59, 33.95) <sup>n</sup>

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; LS = least square; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

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

- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- 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 × LLOQ.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the difference of LS means and corresponding CIs based on analysis of logarithmically transformed neutralizing titres using a linear regression model with terms of baseline neutralizing titre (log scale) and vaccine group or age group.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).
- Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67.
- Superiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 1.
- Noninferiority 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.

- h. N = Number of participants with valid and determinate assay results for the specified assay at both the prevaccination time point and the given sampling time point. This value is the denominator for the percentage calculation.
- i. n = Number of participants with seroresponse for the given assay at the given sampling time point.
- j. Exact 2-sided CI, based on the Clopper and Pearson method.
- k. Difference in proportions, expressed as a percentage.
- l. 2-sided CI based on the Miettinen and Nurminen method stratified by baseline neutralizing titre category (< median, ≥ median) for the difference in proportions. The median of baseline neutralizing titres was calculated based on the pooled data in 2 comparator groups.
- m. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is >-10%.
- n. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is >-5%.

**Table 5: Geometric mean titres – Comirnaty Original/Omicron BA.4-5 subsets of Study 5 –prior to and 1 month after booster (fourth dose) – participants 12 years of age and older – with or without evidence of infection - evaluable immunogenicity population**

SARS-CoV-2 neutralization assay	Sampling time point <sup>a</sup>	Comirnaty Original/Omicron BA.4-5					
		12 through 17 years of age		18 through 55 years of age		56 years of age and older	
		n <sup>b</sup>	GMT <sup>c</sup> (95% CI <sup>c</sup> )	n <sup>b</sup>	GMT <sup>c</sup> (95% CI <sup>c</sup> )	n <sup>b</sup>	GMT <sup>c</sup> (95% CI <sup>c</sup> )
Omicron BA.4-5 - NT50 (titre) <sup>d</sup>	Pre-vaccination	104	1105.8 (835.1, 1464.3)	294	569.6 (471.4, 688.2)	284	458.2 (365.2, 574.8)
	1 month	105	8212.8 (6807.3, 9908.7)	297	4455.9 (3851.7, 5154.8)	284	4158.1 (3554.8, 4863.8)
Reference strain – NT50 (titre) <sup>d</sup>	Pre-vaccination	105	6863.3 (5587.8, 8430.1)	296	4017.3 (3430.7, 4704.1)	284	3690.6 (3082.2, 4419.0)
	1 month	105	23641.3 (20473.1, 27299.8)	296	16323.3 (14686.5, 18142.6)	286	16250.1 (14499.2, 18212.4)

Abbreviations: CI = confidence interval; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- 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 titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
- d. SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4-5).

### **Comirnaty**

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 to 15 years of age, 16 to 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥ 56-year stratum. The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19. Participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrolment, were included as were participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis B virus (HBV).

### *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 44000 participants were randomised equally and were to receive 2 doses of the initially approved 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 36621 participants 12 years of age and older (18242 in the COVID-19 mRNA Vaccine group and 18379 in the placebo group) who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose. In addition, 134 participants were between the ages of 16 to 17 years of age (66 in the COVID-19 mRNA Vaccine group and 68 in the placebo group) and 1616 participants 75 years of age and older (804 in the COVID-19 mRNA Vaccine group and 812 in the placebo group).

At the time of the primary efficacy analysis, participants had been followed for symptomatic COVID-19 for in total 2214 person-years for the COVID-19 mRNA Vaccine and in total 2222 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 6**.

**Table 6: 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**

<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> = 18198 Cases n1<sup>b</sup> Surveillance time<sup>c</sup> (n2<sup>d</sup>)</b>	<b>Placebo N<sup>a</sup> = 18325 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 participants	8 2.214 (17411)	162 2.222 (17511)	95.0 (90.0, 97.9)
16 to 64 years	7 1.706 (13549)	143 1.710 (13618)	95.1 (89.6, 98.1)
65 years and older	1 0.508 (3848)	19 0.511 (3880)	94.7 (66.7, 99.9)
65 to 74 years	1 0.406 (3074)	14 0.406 (3095)	92.9 (53.1, 99.8)
75 years and older	0 0.102 (774)	5 0.106 (785)	100.0 (-13.1, 100.0)

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

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

- 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. 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, representing up to 6 months after Dose 2 in the efficacy population.

The updated vaccine efficacy information is presented in **Table 7**.

**Table 7: Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of prior SARS-CoV-2 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>=20998 Cases n1<sup>b</sup> Surveillance time<sup>c</sup> (n2<sup>d</sup>)</b>	<b>Placebo N<sup>a</sup>=21096 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 participants <sup>f</sup>	77 6.247 (20712)	850 6.003 (20713)	91.3 (89.0, 93.2)
16 to 64 years	70 4.859 (15519)	710 4.654 (15515)	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 to 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)

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 95% confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
- Included confirmed cases in participants 12 to 15 years of age: 0 in the COVID-19 mRNA Vaccine group; 16 in the placebo group.

In the updated efficacy analysis, efficacy of COVID-19 mRNA Vaccine in preventing first COVID-19 occurrence from 7 days after Dose 2 compared to placebo was 91.1% (95% CI of 88.8% to 93.0%) during the period when Wuhan/Wild type and Alpha variants were the predominant circulating strains in participants in the evaluable efficacy population with or without evidence of prior infection with SARS-CoV-2.

Additionally, the updated efficacy analyses by subgroup showed similar efficacy point estimates across sexes, ethnic groups, geography and participants with medical comorbidities and obesity associated with high risk of severe COVID-19.

#### *Efficacy against severe COVID-19*

Updated efficacy analyses of secondary efficacy endpoints supported benefit of the COVID-19 mRNA Vaccine in preventing severe COVID-19.

As of 13 March 2021, vaccine efficacy against severe COVID-19 is presented only for participants with or without prior SARS-CoV-2 infection (**Table 8**) 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 8: Vaccine efficacy – First severe COVID-19 occurrence in participants with or without prior SARS-CoV-2 infection based on the Food and Drug Administration (FDA)\* after Dose 1 or from 7 days after Dose 2 in the placebo-controlled follow-up**

	COVID-19 mRNA Vaccine Cases n1 <sup>a</sup> Surveillance time (n2 <sup>b</sup> )	Placebo Cases n1 <sup>a</sup> Surveillance time (n2 <sup>b</sup> )	Vaccine efficacy % (95% CI <sup>c</sup> )
After Dose 1 <sup>d</sup>	1 8.439 <sup>e</sup> (22505)	30 8.288 <sup>e</sup> (22435)	96.7 (80.3, 99.9)
7 days after Dose 2 <sup>f</sup>	1 6.522 <sup>g</sup> (21649)	21 6.404 <sup>g</sup> (21730)	95.3 (70.9, 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).

\* 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.

- a. n1 = Number of participants meeting the endpoint definition.
- b. n2 = Number of participants at risk for the endpoint.
- c. Two-side confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
- d. Efficacy assessed based on the Dose 1 all available efficacy (modified intention-to-treat) population that included all 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 to 15 years of age – after 2 doses*

In an initial analysis of Study 2 in adolescents 12 to 15 years of age (representing a median follow-up duration of  $>$  2 months after Dose 2) 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).

Updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

In the updated efficacy analysis of Study 2 in adolescents 12 to 15 years of age without evidence of prior infection, there were no cases in 1057 participants who received the vaccine and 28 cases out of 1030 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 86.8, 100.0) during the period when Alpha variant was the predominant circulating strain. In participants with or without evidence of prior infection there were 0 cases in the 1119 who received vaccine and 30 cases in 1109 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 87.5, 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 to 15 years of age (n = 190) to participants 16 to 25 years of age (n = 170).

The ratio of the geometric mean titres (GMT) in the 12 to 15 years of age group to the 16 to 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 noninferiority criterion was met as the lower bound of the 2-sided 95% CI for the geometric mean ratio [GMR] was > 0.67.

*Efficacy and immunogenicity in children 5 to 11 years of age (i.e., 5 to less than 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 to 11 years of age. The majority (94.4%) of randomised vaccine recipients received the second dose 19 days to 23 days after Dose 1.

Initial descriptive vaccine efficacy results in children 5 to 11 years of age without evidence of prior SARS-CoV-2 infection are presented in **Table 9**. 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 9: 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 to 11 years of age evaluable efficacy population**

<b>First COVID-19 occurrence from 7 days after Dose 2 in children 5 to 11 years of age without evidence of prior SARS-CoV-2 infection*</b>			
	<b>COVID-19 mRNA Vaccine 10 mcg/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 to 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.



- 
- 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.

Pre-specified hypothesis-driven efficacy analysis was performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

In the efficacy analysis of Study 3 in children 5 to 11 years of age without evidence of prior infection, there were 10 cases in 2703 participants who received the vaccine and 42 cases out of 1348 who received placebo. The point estimate for efficacy is 88.2% (95% confidence interval 76.2, 94.7) during the period when Delta variant was the predominant circulating strain. In participants with or without evidence of prior infection there were 12 cases in the 3018 who received vaccine and 42 cases in 1511 participants who received placebo. The point estimate for efficacy is 85.7% (95% confidence interval 72.4, 93.2).

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 to 11 years of age (i.e., 5 to less than 12 years of age) in the Phase 2/3 part of Study 3 to participants 16 to 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 geometric mean ratio (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 GMR of the SARS-CoV-2 NT50 1 month after Dose 2 in children 5 to 11 years of age (i.e., 5 to less than 12 years of age) to that of young adults 16 to 25 years of age was 1.04 (2-sided 95% CI: 0.93, 1.18). Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, 99.2% of children 5 to 11 years of age and 99.2% of participants 16 to 25 years of age had a seroresponse at 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%). This information is presented in **Table 10**.

**Table 10: Summary of geometric mean ratio for 50% neutralising titre and difference in percentages of participants with seroresponse – comparison of children 5 to 11 years of age (Study 3) to participants 16 to 25 years of age (Study 2) – participants without evidence of infection up to 1 month after Dose 2 – immunobridging subset – Phase 2/3 – evaluable immunogenicity population**

		COVID-19 mRNA Vaccine		5 to 11 years/ 16 to 25 years	
		10 mcg/dose 5 to 11 years N <sup>a</sup> =264	30 mcg/dose 16 to 25 years N <sup>a</sup> =253		
	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)
Geometric mean 50% neutralising titre <sup>f</sup> (GMT <sup>c</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
	Time point <sup>b</sup>	n <sup>g</sup> (%) (95% CI <sup>h</sup> )	n <sup>g</sup> (%) (95% CI <sup>h</sup> )	Difference % <sup>i</sup> (95% CI <sup>j</sup> )	Met immunobridging objective <sup>k</sup> (Y/N)
Seroresponse rate (%) for 50% neutralising titre <sup>f</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: 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.

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 Dose 1 visit and 1 month after Dose 2, SARS-CoV-2 not detected by NAAT [nasal swab] at Dose 1 and Dose 2 visits, 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.

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.

- N = Number of participants with valid and determinate assay results before vaccination and at 1 month after Dose 2. These values are also the denominators used in the percentage calculations for seroresponse rates.
- Protocol-specified timing for blood sample collection.
- 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.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (5 to 11 years of age minus 16 to 25 years of age) and the corresponding CI (based on the Student t distribution).
- Immunobridging based on GMT 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  $\geq 0.8$ .
- 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.
- n = Number of participants with seroresponse based on NT50 1 month after Dose 2.
- Exact 2-sided CI based on the Clopper and Pearson method.
- Difference in proportions, expressed as a percentage (5 to 11 years of age minus 16 to 25 years of age).
- 2-Sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
- Immunobridging based on seroresponse rate is declared if the lower bound of the 2-sided 95% CI for the seroresponse difference is greater than -10.0%.

*Immunogenicity in children 5 to 11 years of age (i.e., 5 to less than 12 years of age) – after booster dose*  
 A booster dose of Comirnaty was given to 401 randomly selected participants in Study 3. Effectiveness of a booster dose in ages 5 to 11 is inferred by immunogenicity. The immunogenicity of this was assessed through 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 demonstrated a substantial increase in GMTs in individuals 5 through 11 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the dose 2 and the booster dose. This analysis is summarized in **Table 11**.

**Table 11: Summary of geometric mean titres – NT50 – participants without evidence of infection – phase 2/3 – immunogenicity set – 5 through 11 years of age – evaluable immunogenicity population**

Assay	Sampling time point <sup>a</sup>		1 month after booster dose/ 1 month after dose 2
	1 month after booster dose (n <sup>b</sup> =67)	1 month after dose 2 (n <sup>b</sup> =96)	
	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> )
SARS-CoV-2 neutralisation assay - NT50 (titre)	2720.9 (2280.1, 3247.0)	1253.9 (1116.0, 1408.9)	2.17 (1.76, 2.68)

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NT50 = 50% neutralising titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
- 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  $0.5 \times \text{LLOQ}$ .
- GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (1-Month Post-Booster Dose minus 1-Month Post-Dose 2) and the corresponding CI (based on the Student t distribution).

*Efficacy and immunogenicity of a 3-dose primary course in infants and children 6 months to 4 years of age*

The efficacy analysis of Study 3 was performed across the combined population of participants 6 months through 4 years of age based on cases confirmed among 873 participants in the COVID-19 mRNA Vaccine group and 381 participants in the placebo group (2:1 randomization ratio) who received all 3 doses of study intervention during the blinded follow-up period when the Omicron variant of SARS-CoV-2 (BA.2) was the predominant variant in circulation (data cut-off date of 17 June 2022).

The vaccine efficacy results after Dose 3 in participants 6 months through 4 years of age are presented in **Table 12**.

**Table 12: Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 3 – Blinded Follow-Up Period – Participants Without Evidence of Infection Prior to 7 Days After Dose 3 – Phase 2/3 – 6 Months to 4 Years of Age – Evaluable Efficacy (3-Dose) Population**

<b>First COVID-19 occurrence from 7 days after Dose 3 in participants without evidence of prior SARS-CoV-2 infection*</b>			
<b>Subgroup</b>	<b>COVID-19 mRNA Vaccine 3 mcg/Dose N<sup>a</sup>=873 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>=381 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>
6 months through 4 years <sup>c</sup>	13 0.124 (794)	21 0.054 (351)	73.2 (43.8, 87.6)
2 through 4 years	9 0.081 (498)	13 0.033 (204)	71.8 (28.6, 89.4)
6 months through 23 months	4 0.042 (296)	8 0.020 (147)	75.8 (9.7, 94.7)

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

\* Participants who had no serological or virological evidence (prior to 7 days after receipt of Dose 3) of past SARS-CoV-2 infection (i.e., negative N-binding antibody [serum] result at Dose 1, 1 month post-Dose 2 (if available), Dose 3 (if available) visits, SARS-CoV-2 not detected by NAAT [nasal swab] at Dose 1, Dose 2, and Dose 3 study visits, and a negative NAAT [nasal swab] result at any unscheduled visit prior to 7 days after receipt of Dose 3) and had no medical history of COVID-19 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 3 to the end of the surveillance period.
- n<sup>2</sup> = Number of participants at risk for the endpoint.
- Two-sided 95% confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.

Vaccine efficacy in participants with or without prior SARS-CoV-2 infection was similar to those participants without prior SARS-CoV-2 infection.

Severe COVID-19 criteria (as described in the protocol, based on FDA definition and modified for children) were fulfilled for 12 cases (8 COVID-19 mRNA Vaccine and 4 placebo) among participants 6 months to 4 years of age. Among participants 6 months through 23 months of age, severe COVID-19 criteria were fulfilled for 3 cases (2 COVID-19 mRNA Vaccine and 1 placebo).

Immunogenicity analyses have been performed in the immunobridging subset of 82 Study 3 participants 6 to 23 months of age and 143 Study 3 participants 2 to 4 years of age without evidence of infection up to 1 month after Dose 3 based on a data cut-off date of 29 April 2022.

SARS-CoV-2 50% neutralising antibody titres (NT50) were compared between an immunogenicity subset of Phase 2/3 participants 6 to 23 months of age and 2 to 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 to 25 years of age at 1 month after the 2-dose primary course, using a microneutralisation assay against the reference strain (USA\_WA1/2020).

The primary immunobridging analyses compared the geometric mean titres (using a geometric mean ratio [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 to 23 months of age and 2 to 4 years of age and up to 1 month after Dose 2 in participants 16 to 25 years of age. The prespecified immunobridging criteria were met for both the GMR and the seroresponse difference for both age groups (**Table 13**).

**Table 13. SARS-CoV-2 GMTs (NT50) and difference in percentages of participants with seroresponse at 1 month after vaccination course – immunobridging subset - participants 6 months to 4 years of age (Study 3) 1 month after Dose 3 and participants 16 to 25 years of age (Study 2) 1 month after Dose 2 – without evidence of SARS-CoV-2 infection – evaluable immunogenicity population**

<b>SARS-CoV-2 GMTs (NT50) at 1 month after vaccination course</b>							
SARS-CoV-2 neutralization assay - NT50 (titre) <sup>e</sup>							
Age	N <sup>a</sup>	GMT <sup>b</sup> (95% CI <sup>b</sup> ) (1 month after Dose 3)	Age	N <sup>a</sup>	GMT <sup>b</sup> (95% CI <sup>b</sup> ) (1 month after Dose 2)	Age	GMR <sup>c,d</sup> (95% CI)
2 to 4 years	143	1535.2 (1388.2, 1697.8)	16 to 25 years of age	170	1180.0 (1066.6, 1305.4)	2 to 4 years/16 to 25 years of age	1.30 (1.13, 1.50)
6 to 23 months	82	1406.5 (1211.3, 1633.1)	16 to 25 years of age	170	1180.0 (1066.6, 1305.4)	6 to 23 months years/16 to 25 years of age	1.19 (1.00, 1.42)
<b>Difference in percentages of participants with seroresponse at 1 month after vaccination course</b>							
SARS-CoV-2 neutralization assay - NT50 (titre) <sup>e</sup>							
Age	N <sup>a</sup>	n <sup>f</sup> (%) (95% CI <sup>g</sup> ) (1 month after Dose 3)	Age	N <sup>a</sup>	n <sup>f</sup> (%) (95% CI <sup>g</sup> ) (1 month after Dose 2)	Age	Difference in seroresponse rates % <sup>h</sup> (95% CI <sup>j</sup> )
2 to 4 years	141	141(100.0) (97.4, 100.0)	16 to 25 years of age	170	168 (98.8) (95.8, 99.9)	2 to 4 years/16 to 25 years of age	1.2 (1.5, 4.2)
6 to 23 months	80	80 (100.0) (95.5, 100.0)	16 to 25 years of age	170	168 (98.8) (95.8, 99.9)	6 to 23 months years/16 to 25 years of age	1.2 (3.4, 4.2)

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein-binding; NT50 = 50% neutralising titre; 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.

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.

- N = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point for GMTs and number of participants with valid and determinate assay results for the specified assay at both baseline and the given dose/sampling time point for seroresponse rates.
- 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.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (younger age group minus 16 to 25 years of age) and the corresponding CI (based on the Student t distribution).

- 
- d. For each younger age group (2 to 4 years, 6 to 23 months), immunobridging based on GMR 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  $\geq 0.8$ .
  - 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 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.
  - f. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.
  - g. Exact 2-sided CI based on the Clopper and Pearson method.
  - h. Difference in proportions, expressed as a percentage (younger age group minus 16 to 25 years of age).
  - i. 2-sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
  - j. For each younger age group (2 to 4 years, 6 to 23 months), immunobridging based on seroresponse rate 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.

## 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

Trometamol

Trometamol hydrochloride

Sucrose

Water for injections

## **6.2. Incompatibilities**

This medicinal product must not be mixed with other medicinal products except those mentioned in section **6.6. Special Precautions for Disposal and Other Handling**.

## **6.3. Shelf Life**

### **Unopened vial**

#### *Frozen vial*

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

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.

When stored frozen at -90 °C to -60 °C, 10-vial packs of the vaccine can be thawed at 2 °C to 8 °C for 2 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

#### *Thawed vial*

10 weeks storage and transportation at 2 °C to 8 °C within the 18-month shelf life.

- Upon moving the vaccine 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. The expiry date on the outer carton should have been updated to reflect the refrigerated expiry date and the original expiry date should have been crossed out.

Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between 8 °C and 30 °C.

Thawed vials can be handled in room light conditions.

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

#### *Handling of temperature excursions during refrigerated storage*

- Stability data indicate that the unopened vial is stable for up to 10 weeks when stored at temperatures from -2 °C to 2 °C, and within the 10 weeks storage period between 2 °C and 8 °C.
- Stability data indicate the vial can be stored for up to 24 hours at temperatures of 8 °C to 30 °C, including up to 12 hours following first puncture.

This information is intended to guide healthcare professionals only in case of temporary temperature excursion.

### **Diluted medicinal product**

Chemical and physical in-use stability has been demonstrated for 12 hours at 2 °C to 30 °C, after dilution with sodium chloride 9 mg/mL (0.9%) solution for injection, which includes up to 6 hours transportation time. From a microbiological point of view, unless the method of dilution precludes the risk 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**

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

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

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

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

## **6.5. Nature and Contents of Container**

0.48 mL concentrate for dispersion in a 2 mL clear multidose vial (type I glass) with a stopper (synthetic

bromobutyl rubber) and a **yellow flip-off plastic** cap with aluminium seal. Each vial contains **3 doses**, see section **6.6. Special Precautions for Disposal and Other Handling**.

Pack size: 10 vials

## **6.6. Special Precautions for Disposal and Other Handling**

### ***Handling instructions prior to use for a vial with a yellow cap***

Comirnaty JN.1 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- **Verify** that the vial has a **yellow plastic cap** and the product **name is Comirnaty JN.1 (3 micrograms)/dose concentrate for dispersion for injection** (infants and children 6 months to 4 years).
- If the vial has another product name on the label or a different cap colour, please make reference to the product leaflet for that formulation.
- If the 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.
- 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.

### **Dilution for a vial with a yellow cap**

- Allow the thawed vial to come to room temperature and gently invert it 10 times prior to dilution. Do not shake.
- Prior to dilution, the thawed dispersion may contain white to off-white opaque amorphous particles.
- The thawed vaccine must be diluted in its original vial with **1.1 mL sodium chloride 9 mg/mL (0.9%) solution for injection**, using a 21 gauge or narrower needle and aseptic techniques.
- Equalise vial pressure before removing the needle from the vial stopper by withdrawing 1.1 mL air into the empty diluent syringe.
- 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 discolouration are present.
- The diluted vials should be marked with the appropriate **discard date and time**.
- **After dilution**, store at 2 °C to 30 °C and use within **12 hours**.
- Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.

### **Preparation of 0.3 mL doses using a vial with a yellow cap**

- After dilution, the vial contains 1.58 mL from which **3 doses** of **0.3 mL** can be extracted.
- Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
- Withdraw **0.3 mL** of Comirnaty JN.1 for infants and children aged 6 months to 4 years. **Standard syringes and/or needles** can be used in order to extract 3 doses 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 12 hours after dilution.

### **Disposal**

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



**7. MARKETING AUTHORISATION HOLDER**

Pfizer (Thailand) Limited

**8. MARKETING AUTHORISATION NUMBERS**

1C 8/64 (NBC)

**9. DATE OF AUTHORIZATION**

24 June 2021

**10. DATE OF REVISION OF THE TEXT**

29 May 2024

LPD Revision No.: 15.0

LPD Date: May 29, 2024

Country: Thailand

## LABELING INFORMATION

### COMIRNATY™

#### JN.1 (3 micrograms)/dose

Concentrate for dispersion for injection

Infants and children 6 months to 4 years

COVID-19 mRNA Vaccine

Bretovameran

10 Multidose Vials

#### Statement of active substance(s)

After dilution, each vial contains **3 doses of 0.3 mL**.

Each dose (**0.3mL**) contains 3 micrograms of bretovameran.

#### List of Excipients

ALC-0315, ALC-0159, DSPC, Cholesterol, Trometamol, Trometamol hydrochloride, Sucrose, Water for injections.

#### Method and route(s) of administration

**Intramuscular Use** after dilution.

Read the package leaflet before use.

Keep out of the sight and reach of children.

Scan QR code for more information.



Scan QR code for more information

#### MUST BE DILUTED BEFORE USE:

Dilute each vial with **1.1 mL** sodium chloride 9 mg/mL (0.9%) solution for injection.

#### Storage condition

Store at 2 °C to 8 °C after receipt. Do not refreeze.

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

After dilution, store the vaccine at 2 °C to 30 °C and use within 12 hours.

**ยาคควบคุมพิเศษ ใช้เฉพาะสถานพยาบาล**

Reg. No. 1C 8/64 (NBC)

PC:

Lot/EXP (at -90 °C to -60 °C)/SN/mfg

(ยาลิ้นอาชู)

Expiry date at 2 °C to 8 °C ..... (Maximum 10 weeks; Cross out former expiry date)

#### Manufactured by:

- Pfizer Manufacturing Belgium NV, Puurs-Sint-Amands, Belgium
- BioNTech Manufacturing Marburg GmbH, Marburg Germany
- mibe GmbH Arzneimittel, Brehna Germany

#### Released by:

- Pfizer Manufacturing Belgium NV, Puurs-Sint-Amands, Belgium
- BioNTech Manufacturing GmbH, Mainz, Germany

#### Imported by:

Pfizer (Thailand) Limited  
Bangkok, Thailand