



**FOR 5 TO 11 YEARS OF AGE  
DO NOT DILUTE**

## COMIRNATY™

### 1. NAME OF THE MEDICINAL PRODUCT

Comirnaty™  
JN.1 (10 micrograms)/dose  
Dispersion for injection  
COVID-19 mRNA Vaccine

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

This is a single dose with a blue cap. Do not dilute prior to use.

One single dose vial contains 1 dose of 0.3 mL, 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 10 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

Dispersion for injection.  
The vaccine is a clear to slightly opalescent suspension (pH: 6.9 - 7.9).

### 4. CLINICAL PARTICULARS

#### 4.1. Therapeutic Indications

Comirnaty JN.1 (10 micrograms)/dose dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in children aged 5 to 11 years.

#### 4.2. Posology and Method of Administration

##### Posology

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

Comirnaty JN.1 (10 micrograms)/dose dispersion for injection is administered intramuscularly as a single dose of 0.3 mL for children 5 to 11 years of age regardless of prior COVID-19 vaccination status (see sections **4.4. Special Warnings and Precautions for Use** and **5.1. Pharmacodynamic Properties**).

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 5 years and older***

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**).

Comirnaty JN.1 (10 micrograms)/dose should be used only for children 5 to 11 years of age.

### ***Paediatric population***

There are paediatric formulations available for infants and children aged 6 months to 4 years. 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 (10 micrograms)/dose dispersion for injection should be administered intramuscularly (see section **6.6. Special Precautions for Disposal and Other Handling**). Do not dilute prior to use.

The preferred site is the deltoid muscle of the upper arm (see section **6.6. Special Precautions for Disposal and Other Handling**).

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, handling and disposal of the vaccine, see section **6.6. Special Precautions for Disposal and Other Handling**.

Single dose vials of Comirnaty JN.1 contain 1 dose of 0.3 mL of vaccine.

- Withdraw a single 0.3 mL dose of Comirnaty JN.1.
- Discard vial and any excess volume.

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.

### **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**

### **Pregnancy**

No data are available yet regarding the use of Comirnaty JN.1 during pregnancy.

However, a large amount of observational data from pregnant women vaccinated with the initially approved Comirnaty vaccine during the second and third trimester have not shown an increase in adverse pregnancy outcomes. While data on pregnancy outcomes following vaccination during the first trimester

are presently limited, no increased risk for miscarriage has been seen. 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. Preclinical Safety Data**). Based on data available with other vaccine variants, Comirnaty JN.1 can be used during pregnancy.

### **Breast-feeding**

No data are available yet regarding the use of Comirnaty JN.1 during breast-feeding.

However, no effects on the breast-fed newborn/infant are anticipated since the systemic exposure of breast-feeding woman to the vaccine is negligible. Observational data from women who were breast-feeding after vaccination with the initially approved Comirnaty vaccine have not shown a risk for adverse effects in breast-fed newborns/infants. Comirnaty JN.1 can be used during breast-feeding.

### **Fertility**

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

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

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

### **4.8. Undesirable Effects**

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

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

#### *Comirnaty*

##### *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 the initially approved Comirnaty vaccine 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***

*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 mcg) 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 5 years 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 5 years of age and older**

| <b>System Organ Class</b>            | <b>Frequency</b> | <b>Adverse reactions</b>   |
|--------------------------------------|------------------|--|
| Blood and lymphatic system disorders | Common           | Lymphadenopathy <sup>a</sup>   |
| Immune system disorders              | Uncommon         | Hypersensitivity reactions (e.g., rash, pruritus, urticaria <sup>b</sup> , angioedema <sup>b</sup> ) |
|                                      | Not known        | Anaphylaxis  |
| Metabolism and nutrition disorders   | Uncommon         | Decreased appetite   |
| Psychiatric disorders                | Uncommon         | Insomnia   |
| Nervous system disorders             | Very common      | Headache   |
|                                      | 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>  |

| System Organ Class                                   | Frequency   | Adverse reactions  |
|--|-------------|--|
| 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>i</sup>  |
| General disorders and administration site conditions | Very common | Injection site pain; 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>    |

- 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.
- 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 pyrexia was observed after the second dose compared to the first dose.
- Facial swelling in vaccine recipients with a history of injection of dermatological fillers has been reported in the post-marketing phase.
- Injection site redness occurred at a higher frequency (very common) in children 5 to 11 years of age.
- 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

Pharmacotherapeutic 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 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 neutralising 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 2**.

**Table 2: 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 neutralisation 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% neutralising 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  $0.5 \times$  LLOQ.
- d. 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 neutralising titres, postbaseline infection status, and vaccine group as covariates.
- e. 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 through 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% neutralising 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 3**).

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 3**).

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 4**).

**Table 3: 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 neutralisation 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/ $\geq$ 56 years of age | $\geq$ 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>                                      |
| 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 |                                   |   |                           |   |                             |   |  |   |
|---|-----------------------------------|---|---------------------------|---|-----------------------------|---|--|---|
|   | Comirnaty Original/Omicron BA.4-5 |   |                           |   | Subset of Study 4 Comirnaty |   | Age group comparison   | Vaccine group comparison $\geq 56$ years of age |
|   | 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 $\geq 56$ | Comirnaty Original/Omicron BA.4-5 /Comirnaty    |
| SARS-CoV-2 neutralisation assay   | 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>l</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% neutralising titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Seroresponse is defined as achieving a  $\geq 4$ -fold rise from baseline. 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 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 95% CIs were calculated by exponentiating the difference of LS means and corresponding CIs based on analysis of logarithmically transformed neutralising titres using a linear regression model with terms of baseline neutralising 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  $\geq 0.8$ .
- 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.
- n = Number of participants with seroresponse for the given assay at the given sampling time point.
- Exact 2-sided CI, based on the Clopper and Pearson method.
- Difference in proportions, expressed as a percentage.
- 2-sided CI based on the Miettinen and Nurminen method stratified by baseline neutralising titre category ( $<$  median,  $\geq$  median) for the difference in proportions. The median of baseline neutralising titres was calculated based on the pooled data in 2 comparator groups.
- Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is  $> -10\%$ .
- 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 4: 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 neutralisation 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% 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 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  $0.5 \times \text{LLOQ}$ .
- 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  $\geq 56$ -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 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 5**.

**Table 5: 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<br/>N<sup>a</sup> = 18198<br/>Cases<br/>n1<sup>b</sup><br/>Surveillance time<sup>c</sup> (n2<sup>d</sup>)</b> | <b>Placebo<br/>N<sup>a</sup> = 18325<br/>Cases<br/>n1<sup>b</sup><br/>Surveillance time<sup>c</sup> (n2<sup>d</sup>)</b> | <b>Vaccine efficacy %<br/>(95% CI)<sup>e</sup></b> |
| All participants  | 8<br>2.214 (17411)   | 162<br>2.222 (17511)   | 95.0 (90.0, 97.9)                                  |
| 16 to 64 years  | 7<br>1.706 (13549)   | 143<br>1.710 (13618)   | 95.1 (89.6, 98.1)                                  |
| 65 years and older  | 1<br>0.508 (3848)  | 19<br>0.511 (3880)   | 94.7 (66.7, 99.9)                                  |
| 65 to 74 years  | 1<br>0.406 (3074)  | 14<br>0.406 (3095)   | 92.9 (53.1, 99.8)                                  |
| 75 years and older  | 0<br>0.102 (774)   | 5<br>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 6**.

**Table 6: 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**

| Subgroup                      | COVID-19 mRNA Vaccine<br>N <sup>a</sup> =20998<br>Cases<br>n1 <sup>b</sup><br>Surveillance time <sup>c</sup> (n2 <sup>d</sup> ) | Placebo<br>N <sup>a</sup> =21096<br>Cases<br>n1 <sup>b</sup><br>Surveillance time <sup>c</sup> (n2 <sup>d</sup> ) | Vaccine efficacy<br>%<br>(95% CI <sup>e</sup> ) |
|-------------------------------|---|---|---|
| All participants <sup>f</sup> | 77<br>6.247 (20712)   | 850<br>6.003 (20713)  | 91.3<br>(89.0, 93.2)                            |
| 16 to 64 years                | 70<br>4.859 (15519)   | 710<br>4.654 (15515)  | 90.6<br>(87.9, 92.7)                            |
| 65 years and older            | 7<br>1.233 (4192)   | 124<br>1.202 (4226)   | 94.5<br>(88.3, 97.8)                            |
| 65 to 74 years                | 6<br>0.994 (3350)   | 98<br>0.966 (3379)  | 94.1<br>(86.6, 97.9)                            |
| 75 years and older            | 1<br>0.239 (842)  | 26<br>0.237 (847)   | 96.2<br>(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 7**) 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 7: 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<br>Cases<br>n1 <sup>a</sup><br>Surveillance time (n2 <sup>b</sup> ) | Placebo<br>Cases<br>n1 <sup>a</sup><br>Surveillance time (n2 <sup>b</sup> ) | Vaccine efficacy<br>%<br>(95% CI <sup>c</sup> ) |
|----------------------------------|---|---|---|
| After Dose 1 <sup>d</sup>        | 1<br>8.439 <sup>e</sup> (22505)   | 30<br>8.288 <sup>e</sup> (22435)  | 96.7<br>(80.3, 99.9)                            |
| 7 days after Dose 2 <sup>f</sup> | 1<br>6.522 <sup>g</sup> (21649)   | 21<br>6.404 <sup>g</sup> (21730)  | 95.3<br>(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 8**. 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 8: 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<br/>Vaccine<br/>10 mcg/dose<br/>N<sup>a</sup>=1305<br/>Cases<br/>n1<sup>b</sup><br/>Surveillance time<sup>c</sup><br/>(n2<sup>d</sup>)</b> | <b>Placebo<br/>N<sup>a</sup>=663<br/>Cases<br/>n1<sup>b</sup><br/>Surveillance time<sup>c</sup><br/>(n2<sup>d</sup>)</b> | <b>Vaccine efficacy %<br/>(95% CI)</b> |
| Children 5 to 11 years of age  | 3<br>0.322 (1273)   | 16<br>0.159 (637)  | 90.7<br>(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.

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 9**.

**Table 9: 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<br>5 to 11 years<br>N <sup>a</sup> =264 | 30 mcg/dose<br>16 to 25 years<br>N <sup>a</sup> =253 |   |  |
|  | Time point <sup>b</sup> | GMT <sup>c</sup><br>(95% CI <sup>c</sup> )          | GMT <sup>c</sup><br>(95% CI <sup>c</sup> )           | GMR <sup>d</sup><br>(95% CI <sup>d</sup> )          | Met immunobridging objective <sup>e</sup><br>(Y/N) |
| Geometric mean 50% neutralising titre <sup>f</sup> (GMT <sup>c</sup> ) | 1 month after Dose 2    | 1197.6<br>(1106.1, 1296.6)                          | 1146.5<br>(1045.5, 1257.2)                           | 1.04<br>(0.93, 1.18)                                | Y  |
|  | Time point <sup>b</sup> | n <sup>g</sup> (%)<br>(95% CI <sup>h</sup> )        | n <sup>g</sup> (%)<br>(95% CI <sup>h</sup> )         | Difference % <sup>i</sup><br>(95% CI <sup>j</sup> ) | Met immunobridging objective <sup>k</sup><br>(Y/N) |
| Seroresponse rate (%) for 50% neutralising titre <sup>f</sup>          | 1 month after Dose 2    | 262 (99.2)<br>(97.3, 99.9)                          | 251 (99.2)<br>(97.2, 99.9)                           | 0.0<br>(-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.

- a. 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.
- 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 (5 to 11 years of age minus 16 to 25 years of age) and the corresponding CI (based on the Student t distribution).
- e. 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  $\geq 0.8$ .
- 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.
- g. n = Number of participants with seroresponse based on NT50 1 month after Dose 2.
- h. Exact 2-sided CI based on the Clopper and Pearson method.
- i. Difference in proportions, expressed as a percentage (5 to 11 years of age minus 16 to 25 years of age).
- j. 2-Sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
- k. 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 10**.

**Table 10: 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 (n <sup>b</sup> =67) | 1 month after dose 2 (n <sup>b</sup> =96)  | 1 month after booster dose/<br>1 month after dose 2 |
|  | GMT <sup>c</sup><br>(95% CI <sup>c</sup> )      | GMT <sup>c</sup><br>(95% CI <sup>c</sup> ) | GMR <sup>d</sup><br>(95% CI <sup>d</sup> )          |
| SARS-CoV-2 neutralisation assay - NT50 (titre) | 2720.9<br>(2280.1, 3247.0)                      | 1253.9<br>(1116.0, 1408.9)                 | 2.17<br>(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.

- a. Protocol-specified timing for blood sample collection.
- b. n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
- c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the 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 (1-Month Post-Booster Dose minus 1-Month Post-Dose 2) and the corresponding CI (based on the Student t distribution).

## **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.

### **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 single dose vials 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, within the 10-week 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.

#### **Opened vial**

Chemical and physical in-use stability has been demonstrated for 12 hours at 2 °C to 30 °C, which includes up to 6 hours transportation time. From a microbiological point of view, unless the method of opening precludes the risks of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

#### **6.4. Special Precautions for Storage**

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 first opening, see section **6.3. Shelf Life**.

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

Comirnaty JN.1 dispersion is supplied in a 2 mL clear vial (type I glass) with a stopper (synthetic bromobutyl rubber) and a blue flip off plastic cap with aluminium seal.

One single dose vial contains 1 dose of 0.3 mL, see sections **4.2. Posology and Method of Administration** and **6.6. Special Precautions for Disposal and Other Handling**.

Pack size: 10 vials.

Not all pack sizes may be marketed.

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

##### **Handling instructions prior to use**

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 **blue plastic cap** and the **product name is Comirnaty JN.1 (10 micrograms)/dose dispersion for injection** (children 5 to 11 years).
- If the vial has another product name on the label, 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. Ensure vials are completely thawed prior to use.
- A 10-vial pack of single dose vials may take 2 hours to thaw.
- 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.

#### Preparation of 0.3 mL doses

- 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 clear to slightly opalescent dispersion with no particulates visible. Do not use the vaccine if particulates or discolouration are present.
- Withdraw a single 0.3 mL dose of vaccine.
- Discard vial and any excess volume.
- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
- Record the appropriate date/time on the vial. Discard any unused vaccine 12 hours after first puncture.

#### **Disposal**

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

### **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 (10 micrograms)/dose

Dispersion for injection

Children 5 to 11 years

COVID-19 mRNA Vaccine

Bretovameran

10 Single Dose Vials

#### Statement of active substance(s)

One dose (0.3 mL) contains 30 micrograms of bretovameran. Each vial contains 1 doses of 0.3 mL.

#### List of Excipients

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

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

##### Intramuscular Use.

Do not dilute prior to use.

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

#### Storage condition

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

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

#### ยาคควบคุมพิเศษ ใช้เฉพาะสถานพยาบาล

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

PC:

Lot/EXP (at -90 °C to -60 °C)/SN/mfg

(ยาลิ้นอายุ)

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