## 1. NAME OF THE MEDICINAL PRODUCT

Comirnaty Omicron XBB.1.5 dispersion for injection COVID-19 mRNA Vaccine (nucleoside modified) 30 micrograms/dose.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

This is a multidose vial with a grey cap. Do not dilute prior to use.
One multidose vial (2.25 mL) contains 6 doses of 0.3 mL, see sections 4.2 and 6.6.
One dose (0.3 mL) contains 30 micrograms of raxtozinameran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).
Raxtozinameran 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 (Omicron XBB.1.5).
For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

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

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Comirnaty Omicron XBB.1.5 30 micrograms/dose dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 12 years of age and older.
The use of this vaccine should be in accordance with official recommendations.

### 4.2 Posology and method of administration

Posology
*Individuals 12 years of age and older*
Comirnaty Omicron XBB.1.5 30 micrograms/dose is administered intramuscularly as a single dose of 0.3 mL for individuals 12 years of age and older regardless of prior COVID-19 vaccination status (see sections 4.4 and 5.1).
For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty Omicron XBB.1.5 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.
*Severely immunocompromised aged 12 years and older*
Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations (see section 4.4).
*Paediatric population*
Comirnaty Omicron XBB.1.5 dispersion for injection 30 micrograms/dose is not intended for children aged less than 12 years.
*Elderly population*
No dose adjustment is required in elderly individuals ≥ 65 years of age.
Method of administration
Comirnaty Omicron XBB.1.5 30 micrograms/dose dispersion for injection should be administered intramuscularly (see section 6.6). Do not dilute prior to use.
The preferred site is the deltoid muscle of the upper arm.
Do not inject the vaccine intravascularly, subcutaneously or intradermally.
The vaccine should not be mixed in the same syringe with any other vaccines or medicinal products.
For precautions to be taken before administering the vaccine, see section 4.4.
For instructions regarding thawing, handling and disposal of the vaccine, see section 6.6.
*Multidose vials*
Multidose vials of Comirnaty Omicron XBB.1.5 contain 6 doses of 0.3 mL of vaccine. In order to extract 6 doses from a single vial, low dead-volume syringes and/or needles should be used. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial. Irrespective of the type of syringe and needle:

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

### 4.3 Contraindications

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

### 4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.
General recommendations
*Hypersensitivity and anaphylaxis*
Events of anaphylaxis have been reported. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine.
Close observation for at least 15 minutes is recommended following vaccination. 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). 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 Omicron XBB.1.5 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 Omicron XBB.1.5 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 Omicron XBB.1.5 with other vaccines has not been studied.

### 4.6 Fertility, pregnancy and lactation

Pregnancy
No data are available yet regarding the use of Comirnaty Omicron XBB.1.5 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). Based on data available with other vaccine variants, Comirnaty Omicron XBB.1.5 can be used during pregnancy.
Breast-feeding
No data are available yet regarding the use of Comirnaty Omicron XBB.1.5 during breast-feeding.
However, no effects on the breastfed 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 breastfed newborns/infants. Comirnaty Omicron XBB.1.5 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).

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

Comirnaty Omicron XBB.1.5 has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under section 4.8 may temporarily affect the ability to drive or use machines.

### 4.8 Undesirable effects

Summary of safety profile
The safety of Comirnaty Omicron XBB.1.5 is inferred from safety data of the prior Comirnaty vaccines.
*Comirnaty 30 mcg*
*Participants 16 years of age and older – after 2 doses*
In Study 2, a total of 22 026 participants 16 years of age or older received at least 1 dose of the initially approved Comirnaty vaccine and a total of 22 021 participants 16 years of age or older received placebo (including 138 and 145 adolescents 16 and 17 years of age in the vaccine and placebo groups, respectively). A total of 20 519 participants 16 years of age or older received 2 doses of Comirnaty.
At the time of the analysis of Study 2 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 25 651 (58.2%) participants (13 031 Comirnaty and 12 620 placebo) 16 years of age and older were followed up for ≥ 4 months after the second dose. This included a total of 15 111 (7 704 Comirnaty and 7 407 placebo) participants 16 to 55 years of age and a total of 10 540 (5 327 Comirnaty and 5 213 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.
*Adolescents 12 to 15 years of age – after 2 doses*
In an analysis of long-term safety follow-up in Study 2, 2 260 adolescents (1 131 Comirnaty and 1 129 placebo) were 12 to 15 years of age. Of these, 1 559 adolescents (786 Comirnaty and 773 placebo) have been followed for ≥ 4 months after the second dose of Comirnaty. The safety evaluation in Study 2 is ongoing.
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 12 years of age and older – after booster dose*
The safety of a booster dose of Comirnaty in participants 12 years of age and older is inferred from safety data from studies of a booster dose of Comirnaty in participants 16 years of age and older.
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 ≥ 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 (5 081 participants), or placebo (5 044 participants) at least 6 months after the second dose of Comirnaty. Overall, participants who received a booster dose, had a median follow-up time of 2.8 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, 1 281 participants (895 Comirnaty and 386 placebo) have been followed for ≥ 4 months after the booster dose of Comirnaty. No new adverse reactions of Comirnaty were identified.
*Participants 12 years of age and older – after subsequent booster doses*
The safety of a booster dose of Comirnaty in participants 12 years of age and older is inferred from safety data from studies of a booster dose of Comirnaty in participants 18 years of age and older.
A subset of 325 adults 18 to ≤ 55 years of age who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty 90 to 180 days after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty had a median follow-up time of 1.4 months up to a data cut-off date of 11 March 2022. The most frequent adverse reactions in these participants were injection site pain (> 70%), fatigue (> 60%), headache (> 40%), myalgia and chills (> 20%), and arthralgia (> 10%).
In a subset from Study 4 (Phase 3), 305 adults > 55 years of age who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty 5 to 12 months after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty had a median follow-up time of at least 1.7 months up to a data cut-off date of 16 May 2022. The overall safety profile for the Comirnaty booster (fourth dose) was similar to that seen after the Comirnaty booster (third dose). The most frequent adverse reactions in participants > 55 years of age were injection site pain (> 60%), fatigue (> 40%), headache (> 20%), myalgia and chills (> 10%).
*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 (see section 5.1).
*Omicron-adapted Comirnaty*
*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 12 years of age and older
Adverse reactions observed during clinical studies are listed below according to the following frequency categories:
Very common (≥ 1/10),
Common (≥ 1/100 to < 1/10),
Uncommon (≥ 1/1 000 to < 1/100),
Rare (≥ 1/10 000 to < 1/1 000),
Very rare (< 1/10 000),
Not known (cannot be estimated from the available data).

**Table 1. Adverse reactions from Comirnaty and Comirnaty Original/Omicron BA.4-5 clinical trials and Comirnaty post-authorisation experience in individuals 12 years of age and older**

| System Organ Class | Very common (≥ 1/10) | Common (≥ 1/100 to < 1/10) | Uncommon (≥ 1/1,000 to < 1/100) | Rare (≥ 1/10,000 to < 1/1,000) | Very rare (< 1/10,000) | Not known (cannot be estimated from the available data) |
|---|---|---|---|---|---|---|
| Blood and lymphatic system disorders | | Lymphadenopathy[a] | | | | |
| Immune system disorders | | | Hypersensitivity reactions (e.g. rash, pruritus, urticaria[b], angioedema[b]) | | | Anaphylaxis |
| Metabolism and nutrition disorders | | | Decreased appetite | | | |
| Psychiatric disorders | | | Insomnia | | | |
| Nervous system disorders | Headache | | Dizziness[d]; Lethargy | Acute peripheral facial paralysis[c] | | Paraesthesia[d]; Hypoaesthesia[d] |
| Cardiac disorders | | | | | Myocarditis[d]; Pericarditis[d] | |
| Gastrointestinal disorders | Diarrhoea[d] | Nausea; Vomiting[d] | | | | |
| Skin and subcutaneous tissue disorder | | | Hyperhidrosis; Night sweats | | | Erythema multiforme[d] |
| Musculoskeletal and connective tissue disorders | Arthralgia; Myalgia | | Pain in extremity[e] | | | |
| Reproductive system and breast disorders | | | | | | Heavy menstrual bleeding[h] |
| General disorders and administration site conditions | Injection site pain; Fatigue; Chills; Pyrexia[f]; Injection site swelling | Injection site redness | Asthenia; Malaise; Injection site pruritus | | | Extensive swelling of vaccinated limb[d]; Facial swelling[g] |

a. In participants 5 years of age and older, a higher frequency of lymphadenopathy was reported after a booster (≤ 2.8%) dose than after primary (≤ 0.9%) doses of the vaccine.
b. The frequency category for urticaria and 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. 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).
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 10 000 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 10 000 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. Healthcare professionals are asked to report any suspected adverse reactions to local regulatory authorities per the local requirements and include batch/Lot number if available.

### 4.9 Overdose

Overdose data is available from 52 study participants included in the clinical trial that due to an error in dilution received 58 micrograms of Comirnaty. The vaccine recipients did not report an increase in reactogenicity or adverse reactions.
In the event of overdose, monitoring of vital functions and possible symptomatic treatment is recommended.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vaccines, 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 neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19.
Efficacy
*Omicron-adapted Comirnaty*
*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 to 17 years of age, 18 to 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 2).
Analyses of NT50 against Omicron BA.4/BA.5 among participants 18 to 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 to 55 years of age compared to participants 56 years of age and older for both GMR and difference in seroresponse rates (Table 2).
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 3).

**Table 2. 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 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 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 |
| SARS-CoV-2 neutralization assay | n[a] | GMT[c] (95% CI[c]) | n[a] | GMT[b] (95% CI[b]) | n[a] | GMT[b] (95% CI[b]) | GMR[c] (95% CI[c]) | GMR[c] (95% CI[c]) |
| Omicron BA.4-5 - NT50 (titre)[d] | 297 | 4 455.9 (3 851.7, 5 154.8) | 284 | 4 158.1 (3 554.8, 4 863.8) | 282 | 938.9 (802.3, 1 098.8) | 0.98 (0.83, 1.16)[e] | 2.91 (2.45, 3.44)[f] |
| Reference Strain – NT50 (titre)[d] | – | – | 286 | 16 250.1 (14 499.2, 18 212.4) | 289 | 10 415.5 (9 366.7, 11 581.8) | – | 1.38 (1.22, 1.56)[g] |
| **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 ≥ 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/≥ 56 | Comirnaty Original/ Omicron BA.4-5 /Comirnaty |
| SARS-CoV-2 neutralization assay | N[h] | n[i] (%) (95% CI[k]) | N[h] | n[i] (%) (95% CI[k]) | N[h] | n[i] (%) (95% CI[j]) | Difference[k] (95% CI[l]) | Difference[k] (95% CI[l]) |
| Omicron BA.4-5 - NT50 (titre)[d] | 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)[m] | 26.77 (19.59, 33.95)[n] |

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.
a. n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
b. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
c. 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.
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/BA.5).
e. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67.
f. Superiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 1.
g. 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 3. 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[a] | 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[b] | GMT[c] (95% CI[c]) | n[b] | GMT[c] (95% CI[c]) | n[b] | GMT[c] (95% CI[c]) |
| Omicron BA.4-5 - NT50 (titre)[d] | Prevaccination | 104 | 1 105.8 (835.1, 1 464.3) | 294 | 569.6 (471.4, 688.2) | 284 | 458.2 (365.2, 574.8) |
| | 1 month | 105 | 8 212.8 (6 807.3, 9 908.7) | 297 | 4 455.9 (3 851.7, 5 154.8) | 284 | 4 158.1 (3 554.8, 4 863.8) |
| Reference Strain – NT50 (titre)[d] | Prevaccination | 105 | 6 863.3 (5 587.8, 8 430.1) | 296 | 4 017.3 (3 430.7, 4 704.1) | 284 | 3 690.6 (3 082.2, 4 419.0) |
| | 1 month | 105 | 23 641.3 (20 473.1, 27 299.8) | 296 | 16 323.3 (14 686.5, 18 142.6) | 286 | 16 250.1 (14 499.2, 18 212.4) |

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 30 mcg*
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 44 000 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 36 621 participants 12 years of age and older (18 242 in the COVID-19 mRNA Vaccine group and 18 379 in the placebo group) who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose.
In addition, 134 participants were between the ages of 16 to 17 years of age (66 in the COVID-19 mRNA Vaccine group and 68 in the placebo group) and 1 616 participants 75 years of age and older (804 in the COVID-19 mRNA Vaccine group and 812 in the placebo group).
At the time of the primary efficacy analysis, participants had been followed for symptomatic COVID-19 for in total 2 214 person-years for the COVID-19 mRNA Vaccine and in total 2 222 person-years in the placebo group.
There were no meaningful clinical differences in overall vaccine efficacy in participants who were at risk of severe COVID-19 including those with 1 or more comorbidities that increase the risk of severe COVID-19 (e.g. asthma, body mass index (BMI) ≥ 30 kg/m², chronic pulmonary disease, diabetes mellitus, hypertension).
The vaccine efficacy information is presented in Table 4.

**Table 4. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of infection prior to 7 days after Dose 2 – evaluable efficacy (7 days) population**

| First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection* | | | |
|---|---|---|---|
| **Subgroup** | **COVID-19 mRNA Vaccine N[a] = 18 198 Cases n1[b] Surveillance time[c] (n2[d])** | **Placebo N[a] = 18 325 Cases n1[b] Surveillance time[c] (n2[d])** | **Vaccine efficacy % (95% CI)[e]** |
| All participants | 8<br>2.214 (17 411) | 162<br>2.222 (17 511) | 95.0<br>(90.0, 97.9) |
| 16 to 64 years | 7<br>1.706 (13 549) | 143<br>1.710 (13 618) | 95.1<br>(89.6, 98.1) |
| 65 years and older | 1<br>0.508 (3 848) | 19<br>0.511 (3 880) | 94.7<br>(66.7, 99.9) |
| 65 to 74 years | 1<br>0.406 (3 074) | 14<br>0.406 (3 095) | 92.9<br>(53.1, 99.8) |
| 75 years and older | 0<br>0.102 (774) | 5<br>0.106 (785) | 100.0<br>(-13.1, 100.0) |

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

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

a. N = Number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Two-sided confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time. 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 5.

**Table 5. 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 N[a] = 20 998 Cases n1[b] Surveillance time[c] (n2[d])** | **Placebo N[a] = 21 096 Cases n1[b] Surveillance time[c] (n2[d])** | **Vaccine efficacy % (95% CI[e])** |
|---|---|---|---|
| All participants[f] | 77<br>6.247 (20 712) | 850<br>6.003 (20 713) | 91.3<br>(89.0, 93.2) |
| 16 to 64 years | 70<br>4.859 (15 519) | 710<br>4.654 (15 515) | 90.6<br>(87.9, 92.7) |
| 65 years and older | 7<br>1.233 (4 192) | 124<br>1.202 (4 226) | 94.5<br>(88.3, 97.8) |
| 65 to 74 years | 6<br>0.994 (3 350) | 98<br>0.966 (3 379) | 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.

a. N = Number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Two-sided 95% confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
f. Included confirmed cases in participants 12 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 6) 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 6. 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[a] Surveillance time (n2[b])** | **Placebo Cases n1[a] Surveillance time (n2[b])** | **Vaccine efficacy % (95% CI[c])** |
|---|---|---|---|
| After Dose 1[d] | 1<br>8.439[e] (22 505) | 30<br>8.288[e] (22 435) | 96.7<br>(80.3, 99.9) |
| 7 days after Dose 2[f] | 1<br>6.522[g] (21 649) | 21<br>6.404[g] (21 730) | 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 ≥ 30 breaths per minute, heart rate ≥ 125 beats per minute, saturation of oxygen ≤ 93% on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen < 300 mm Hg);
- Respiratory failure [defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
- Evidence of shock (systolic blood pressure < 90 mm Hg, diastolic blood pressure < 60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an Intensive Care Unit;
- Death.

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 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 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 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

*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 1 005 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 1 119 who received vaccine and 18 cases in 1 110 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 1 057 participants who received the vaccine and 28 cases out of 1 030 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 1 119 who received vaccine and 30 cases in 1 109 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.

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

Effectiveness of a booster dose of Comirnaty was based on an assessment of 50% neutralizing antibody titres (NT50) against SARS-CoV-2 (USA_WA1/2020) in Study 2. In this study, the booster dose was administered 5 to 8 months (median 7 months) after the second dose. In Study 2, analyses of NT50 1 month after the booster dose compared to 1 month after the primary series in individuals 18 through 55 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the booster vaccination demonstrated noninferiority for both geometric mean ratio (GMR) and difference in seroresponse rates. Seroresponse for a participant was defined as achieving a ≥ 4-fold rise in NT50 from baseline (before primary series). These analyses are summarized in Table 7.

**Table 7. SARS-CoV-2 neutralization assay - NT50 (titre)[†] (SARS-CoV-2 USA_WA1/2020) – GMT and seroresponse rate comparison of 1 month after booster dose to 1 month after primary series – participants 18 through 55 years of age without evidence of infection up to 1 month after booster dose* – booster dose evaluable immunogenicity population[±]**

| | **n** | **1 month after booster dose (95% CI)** | **1 month after primary series (95% CI)** | **1 month after booster dose - 1 month after primary series (97.5% CI)** | **Met noninferiority objective (Y/N)** |
|---|---|---|---|---|---|
| **Geometric mean 50% neutralizing titre (GMT[b])** | 212[a] | 2 466.0[b]<br>(2 202.6, 2 760.8) | 755.7[b]<br>(663.1, 861.2) | 3.26[c]<br>(2.76, 3.86) | Y[d] |
| **Seroresponse rate (%) for 50% neutralizing titre[†]** | 200[e] | 199[f]<br>99.5%<br>(97.2%, 100.0%) | 190[f]<br>95.0%<br>(91.0%, 97.6%) | 4.5%[g]<br>(1.0%, 7.9%[h]) | Y[i] |

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

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

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

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

a. n = Number of participants with valid and determinate assay results at both sampling time points within specified window.
b. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
c. GMRs and 2-sided 97.5% CIs were calculated by exponentiating the mean differences in the logarithms of the assay and the corresponding CIs (based on the Student t distribution).
d. Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the GMR is > 0.67 and the point estimate of the GMR is ≥ 0.80.
e. n = Number of participants with valid and determinate assay results for the specified assay at baseline, 1 month after Dose 2 and 1 month after the booster dose within specified window. These values are the denominators for the percentage calculations.
f. Number of participants with seroresponse for the given assay at the given dose/sampling time point. Exact 2-sided CI based on the Clopper and Pearson method.
g. Difference in proportions, expressed as a percentage (1 month after booster dose – 1 month after Dose 2).
h. Adjusted Wald 2-sided CI for the difference in proportions, expressed as a percentage.
i. Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the percentage difference is > -10%.

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

An interim efficacy analysis of Study 4, a placebo-controlled booster study performed in approximately 10 000 participants 16 years of age and older who were recruited from Study 2, evaluated confirmed COVID-19 cases accrued from at least 7 days after booster vaccination up to a data cut-off date of 5 October 2021, which represents a median of 2.5 months post-booster follow-up. The booster dose was administered 5 to 13 months (median 11 months) after the second dose. Vaccine efficacy of the Comirnaty booster dose after the primary series relative to the placebo booster group who only received the primary series dose was assessed.

The relative vaccine efficacy information for participants 16 years of age and older without prior evidence of SARS-CoV-2 infection is presented in Table 8. Relative vaccine efficacy in participants with or without evidence of prior SARS-CoV-2 infection was 94.6% (95% confidence interval of 88.5% to 97.9%), similar to that seen in those participants without evidence of prior infection. Primary COVID-19 cases observed from 7 days after booster vaccination were 7 primary cases in the Comirnaty group, and 124 primary cases in the placebo group.

**Table 8. Vaccine efficacy – First COVID-19 occurrence from 7 days after booster vaccination – participants 16 years of age and older without evidence of infection – evaluable efficacy population**

| First COVID-19 occurrence from 7 days after booster dose in participants without evidence of prior SARS-CoV-2 infection* | | | |
|---|---|---|---|
| | **Comirnaty N[a] = 4 695 Cases n1[b] Surveillance time[c] (n2[d])** | **Placebo N[a] = 4 671 Cases n1[b] Surveillance time[c] (n2[d])** | **Relative Vaccine Efficacy[e] % (95% CI[f])** |
| First COVID-19 occurrence from 7 days after booster vaccination | 6<br>0.823 (4 659) | 123<br>0.792 (4 614) | 95.3<br>(89.5, 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 serological or virological evidence (prior to 7 days after receipt of the booster vaccination) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visit 1, and had a negative NAAT [nasal swab] at any unscheduled visit prior to 7 days after booster vaccination) were included in the analysis.

a. N = Number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after the booster vaccination to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Relative vaccine efficacy of the Comirnaty booster group relative to the placebo group (non-booster).
f. Two-sided confidence interval (CI) for relative vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.

*Immunogenicity of a booster dose following primary vaccination with another authorised COVID-19 vaccine*

Effectiveness of a Comirnaty booster dose (30 mcg) in individuals who completed primary vaccination with another authorised COVID-19 vaccine (heterologous booster dose) is inferred from immunogenicity data from an independent National Institutes of Health (NIH) study phase 1/2 open-label clinical trial (NCT04889209) conducted in the United States. In this study, adults (range 19 to 80 years of age) who had completed primary vaccination with Moderna 100 mcg 2-dose series (N = 51, mean age 54±17), Janssen single dose (N = 53, mean age 48±14), or Comirnaty 30 mcg 2-dose series (N = 50, mean age 50±18) at least 12 weeks prior to enrolment and who reported no history of SARS-CoV-2 infection received a booster dose of Comirnaty (30 mcg). The boost with Comirnaty induced a 36, 12, and 20 GMR-fold rise in neutralising titres following the Janssen, Moderna, and Comirnaty primary doses, respectively.

Heterologous boosting with Comirnaty was also evaluated in the CoV-BOOST study (EudraCT 2021-002175-19), a multicentre, randomised, controlled, phase 2 trial of third dose booster vaccination against COVID-19, in which 107 adult participants (median age 71 years of age, interquartile range 54 to 77 years of age) were randomised at least 70 days post 2 doses of AstraZeneca COVID-19 Vaccine. After the AstraZeneca COVID-19 Vaccine primary series, pseudovirus (wild-type), neutralising antibody NT50 GMR-fold change increased 21.6-fold with heterologous Comirnaty booster (n = 95).

*Immunogenicity in participants > 55 years of age – after a booster dose (fourth dose) of Comirnaty (30 mcg)*

In an interim analysis of a subset from Study 4 (Substudy E), 305 participants > 55 years of age who had completed a series of 3 doses of Comirnaty received Comirnaty (30 mcg) as a booster dose (fourth dose) 5 to 12 months after receiving Dose 3. For the Immunogenicity subset data see Table 7.

*Immunogenicity in participants 18 to ≤ 55 years of age – after a booster dose (fourth dose) of Comirnaty (30 mcg)*

In Substudy D [a subset from Study 2 (Phase 3) and Study 4 (Phase 3)], 325 participants 18 to ≤ 55 years of age who had completed 3 doses of Comirnaty received Comirnaty (30 mcg) as a booster dose (fourth dose) 90 to 180 days after receiving Dose 3. For the Immunogenicity subset data see Table 9.

**Table 9. Summary of immunogenicity data from participants in C4591031 Substudy D (cohort 2 full expanded set) and Substudy E (expanded cohort immunogenicity subset) who received Comirnaty 30 mcg as booster (fourth dose) – participants without evidence of infection up to 1 month after booster dose – evaluable immunogenicity population**

| | **Dose/ sampling time point[a]** | **Substudy D (18 to ≤ 55 years of age) Comirnaty 30 mcg** | | **Substudy E (> 55 years of age) Comirnaty 30 mcg** | |
|---|---|---|---|---|---|
| **GMT** | | **N[b]** | **GMT (95% CI[d])** | **N[b]** | **GMT (95% CI[d])** |
| SARS-CoV-2 neutralization assay – Omicron BA.1 – NT50 (titre) | 1/Prevax | 226 | 315.0<br>(269.0, 368.9) | 167 | 67.5<br>(52.9, 86.3) |
| | 1/1 Month | 228 | 1 063.2<br>(935.8, 1 207.9) | 163 | 455.8<br>(365.9, 567.6) |
| SARS-CoV-2 neutralization assay – reference strain – NT50 (titre) | 1/Prevax | 226 | 3 999.0<br>(3 529.5, 4 531.0) | 179 | 1 389.1<br>(1 142.1, 1 689.5) |
| | 1/1 Month | 227 | 12 009.9<br>(10 744.3, 13 424.6) | 182 | 5 998.1<br>(5 223.6, 6 887.4) |
| **Seroresponse rate at 1 month post-Dose 4** | | **N[c]** | **n[e] (%) (95% CI[f])** | **N[c]** | **n[e] (%) (95% CI[f])** |
| SARS-CoV-2 neutralization assay – Omicron BA.1 – NT50 (titre) | 1/1 Month | 226 | 91 (40.3%)<br>(33.8, 47.0) | 149 | 85 (57.0%)<br>(48.7, 65.1) |
| SARS-CoV-2 neutralization assay – reference strain – NT50 (titre) | 1/1 Month | 225 | 76 (33.8%)<br>(27.6, 40.4) | 179 | 88 (49.2%)<br>(41.6, 56.7) |

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

Note: Median time from Dose 3 to Dose 4 of Comirnaty 30 mcg is 4.0 months for Substudy D Cohort 2 and 6.3 months for Substudy E expanded cohort.

Note: Substudy D Full Expanded Set = Cohort 2 excluding the sentinel group; Substudy E Immunogenicity Subset = a random sample of 230 participants in each vaccine group selected from the expanded cohort.

Note: Participants who had no serological or virological evidence (prior to the 1-month post–study vaccination blood sample collection) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] result negative at the study vaccination and the 1-month post–study vaccination visits, negative NAAT [nasal swab] result at the study vaccination visit, and any unscheduled visit prior to the 1-month post–study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.

Note: Seroresponse is defined as achieving ≥ 4-fold rise from baseline (before the study vaccination). If the baseline measurement is below the LLOQ, the post-vaccination measure of ≥ 4 × LLOQ is considered a seroresponse.

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. N = Number of participants with valid and determinate assay results for the specified assay at both the pre-vaccination time point and the given sampling time point.
d. 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.
e. n = Number of participants with seroresponse for the given assay at the given sampling time point.
f. Exact 2-sided CI, based on the Clopper and Pearson method.

## 5.2 Pharmacokinetic properties

Not applicable.

## 5.3 Preclinical safety data

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

General toxicity

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

Genotoxicity/Carcinogenicity

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

Reproductive toxicity

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

# 6. PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

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

*Multidose vials*

When stored frozen at -90 °C to -60 °C, 10-vial packs of multidose vials of the vaccine can be thawed at 2 °C to 8 °C for 6 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 ºC to 30 ºC, 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.

## 6.5 Nature and contents of container

Comirnaty Omicron XBB.1.5 dispersion is supplied in a 2 mL clear vial (type I glass) with a stopper (synthetic bromobutyl rubber) and a grey flip-off plastic cap with aluminium seal.

One multidose vial (2.25 mL) contains 6 doses of 0.3 mL, see sections 4.2 and 6.6.

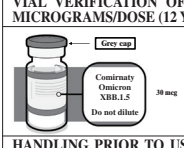
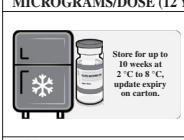
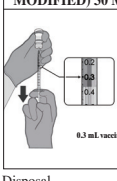
Multidose vial pack sizes: 1 vial, 5 vials or 10 vials.

Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal and other handling

Handling instructions

Comirnaty Omicron XBB.1.5 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

| **VIAL VERIFICATION OF COMIRNATY OMICRON XBB.1.5 DISPERSION FOR INJECTION COVID-19 mRNA VACCINE (NUCLEOSIDE MODIFIED) 30 MICROGRAMS/DOSE (12 YEARS AND OLDER)** | |
|---|---|
|  | • **Verify that the vial has a grey plastic cap and the product name is Comirnaty Omicron XBB.1.5 30 mcg injection.**<br>• Follow the applicable handling instructions below.<br>• If the vial has another product name on the label, please make reference to the Package Insert for that formulation. |
| **HANDLING PRIOR TO USE OF COMIRNATY OMICRON XBB.1.5 DISPERSION FOR INJECTION COVID-19 mRNA VACCINE (NUCLEOSIDE MODIFIED) 30 MICROGRAMS/DOSE (12 YEARS AND OLDER)** | |
|  | • If the multidose vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw. Ensure vials are completely thawed prior to use.<br>o Multidose vials: A 10-vial pack of multidose vials may take 6 hours to thaw.<br>• Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.<br>• Unopened vials can be stored for up to 10 weeks at 2 °C to 8 °C; not exceeding the printed expiry date (EXP).<br>• Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.<br>• 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. |
|  | • Gently mix by inverting vials 10 times prior to use. Do not shake.<br>• Prior to mixing, the thawed dispersion may contain white to off-white opaque amorphous particles.<br>• After mixing, the vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the vaccine if particulates or discolouration are present. |
| **PREPARATION OF INDIVIDUAL 0.3 mL DOSES OF COMIRNATY OMICRON XBB.1.5 DISPERSION FOR INJECTION COVID-19 mRNA VACCINE (NUCLEOSIDE MODIFIED) 30 MICROGRAMS/DOSE (12 YEARS AND OLDER)** | |
|  | Multidose vials<br>• Multidose vials contain 6 doses of 0.3 mL each.<br>• Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.<br>• Withdraw 0.3 mL of Comirnaty Omicron XBB.1.5.<br>Low dead-volume syringes and/or needles should be used in order to extract 6 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres.<br>If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial.<br>• Each dose must contain 0.3 mL of vaccine.<br>• 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.<br>• 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.

**DATE OF REVISION OF THE TEXT**

19 Oct 2023

**For any product enquiries, please call +852-800938618, or email to: infohk@fosunpharma.com.**