WHO PRODUCT INFORMATION

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Comirnaty JN.1 30 micrograms/dose dispersion for injection
Comirnaty JN.1 10 micrograms/dose dispersion for injection
COVID-19 mRNA Vaccine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Do not dilute prior to use.

Table 1. Comirnaty JN.1 qualitative and quantitative composition

Product presentation	**Container**	**Dose(s) per container (see sections 4.2 and 6.6)**	**Contents per dose**
Comirnaty JN.1 30 micrograms/dose dispersion for injection	Single dose vial (grey cap)	1 dose of 0.3 mL	One dose (0.3 mL) contains 30 micrograms of bretovameran, a COVID−19 mRNA Vaccine (nucleoside modified, embedded in lipid nanoparticles).
	Multidose (2.25 mL) vial (grey cap)	6 doses of 0.3 mL	
Comirnaty JN.1 10 micrograms/dose dispersion for injection	Single dose vial (blue cap)	1 dose of 0.3 mL	One dose (0.3 mL) contains 10 micrograms of bretovameran, a COVID−19 mRNA Vaccine (nucleoside modified, embedded in lipid nanoparticles).
	Multidose (2.25 mL) vial (blue cap)	6 doses of 0.3 mL	

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 (Omicron JN.1).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersion for injection.

Comirnaty JN.1 30 micrograms/dose dispersion for injection is a white to off-white dispersion (pH: 6.9 - 7.9).

Comirnaty JN.1 10 micrograms/dose dispersion for injection is a clear to slightly opalescent dispersion (pH: 6.9 - 7.9).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Comirnaty JN.1 dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 5 years of age and older.

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

4.2 Posology and method of administration

Posology

Individuals 12 years of age and older
Comirnaty JN.1 30 micrograms/dose dispersion for injection 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 JN.1 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

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 and 5.1).

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 individuals
Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations (see section 4.4).

Paediatric population
There are paediatric formulations available for infants and children aged 6 months to 4 years. For details, please refer to the WHO Product Information for other formulations.

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

Elderly population
No dose adjustment is required in elderly individuals 65 years of age and older.

Method of administration

Comirnaty JN.1 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.

Single dose vials
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.
- Do not pool excess vaccine from multiple vials.

Multidose vials
Multidose vials of Comirnaty JN.1 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
Safety and immunogenicity have been assessed in a limited number of immunocompromised individuals, including those receiving immunosuppressant therapy (see sections 4.8 and 5.1). 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

Comirnaty JN.1 30 micrograms/dose dispersion for injection may be administered concomitantly with seasonal influenza vaccine.

In individuals 18 years of age and older, Comirnaty JN.1 may be administered concomitantly with a pneumococcal conjugate vaccine (PCV).

In individuals 18 years of age and older, Comirnaty JN.1 may be administered concomitantly with an unadjuvanted recombinant protein respiratory syncytial virus (RSV) vaccine.

In individuals 65 years of age and older, Comirnaty JN.1 may be administered concomitantly with an unadjuvanted recombinant protein RSV vaccine and a high dose influenza vaccine.

Different injectable vaccines should be administered at different injection sites.

Concomitant administration of Comirnaty JN.1 10 micrograms/dose dispersion for injection 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, there are limited clinical study data (less than 300 pregnancy outcomes) from the use of Comirnaty in pregnant participants. 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 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 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 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).

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 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 vaccines.

Initially approved Comirnaty vaccine
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 3 109 children 5 to 11 years of age received at least 1 dose of the initially approved Comirnaty vaccine 10 mcg and a total of 1 538 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, 2 206 (1 481 Comirnaty 10 mcg and 725 placebo) children have been followed for ≥ 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 (≥ 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 2 408 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, 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.

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 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.

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 ≥ 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.

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.

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.

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 6.3 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 myalgia (> 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%), myalgia (> 20%), chills (> 10%), and arthralgia (> 10%).

Participants 12 years of age and older – after a booster dose of Comirnaty Omicron XBB.1.5 (fourth dose or more)
In a subset from Study 13 (Phase 2/3), 412 participants 12 years of age and older, who had received at least 3 doses of an authorised mRNA COVID-19 vaccine, received a booster (fourth dose or more) of Comirnaty Omicron XBB.1.5 2.0 to 24.1 months after receiving Dose 3. Participants who received a booster (fourth dose or more) of Comirnaty XBB.1.5 had a median follow-up time of 6.3 months.

The safety profile of Comirnaty Omicron XBB.1.5 was similar to the overall Comirnaty safety profile.

Participants 12 years of age and older – after a single dose of Comirnaty Omicron XBB.1.5
In a subset from Study 13 (Phase 2/3), 311 participants 12 years of age and older who were considered to be baseline SARS-CoV-2 positive and COVID-19 vaccine-naïve, received 1 dose of Comirnaty Omicron XBB.1.5. Participants had a median follow-up time of 6.4 months.

The safety profile of Comirnaty Omicron XBB.1.5 was similar to the overall Comirnaty safety profile. The most frequent adverse reactions in participants were injection site pain (> 50%), fatigue (> 30%), headache (> 20%), myalgia, diarrhoea, arthralgia, chills and injection site swelling (> 10%).

Participants 12 years of age and older – after a single dose of Comirnaty Omicron JN.1
In a subset from Study 13 (Phase 2/3), 216 participants 12 years of age and older received 1 dose of Comirnaty Omicron JN.1 and had a median follow-up time of 6.3 months.

The safety profile of Comirnaty Omicron JN.1 was similar to the overall Comirnaty safety profile. The most frequent adverse reactions in participants were injection site pain (> 60%), fatigue (> 30%), headache (> 20%), myalgia, chills and injection site swelling (> 10%).

Participants 18 years of age and older – after a single dose of Comirnaty Omicron KP.2
In a subset from Study 13 (Phase 2/3), 102 participants 18 years of age and older received 1 dose of Comirnaty Omicron KP.2 and had a median follow-up time of 6.3 months.

The safety profile of Comirnaty Omicron KP.2 was similar to the overall Comirnaty safety profile. The most frequent adverse reactions in participants were injection site pain (> 50%), fatigue (> 40%), headache and myalgia (> 20%).

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 and post-authorisation experience 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 2. 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

System Organ Class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Common	Lymphadenopathy[a]
Immune system disorders	Uncommon	Hypersensitivity reactions (e.g. rash, pruritus, urticaria[b], angioedema[b])
	Not known	Anaphylaxis
Metabolism and nutrition disorders	Uncommon	Decreased appetite
Psychiatric disorders	Uncommon	Insomnia
Nervous system disorders	Very common	Headache
	Uncommon	Dizziness[d]; lethargy
	Rare	Acute peripheral facial paralysis[c]
	Not known	Paraesthesia[d]; hypoaesthesia[d]
Cardiac disorders	Very rare	Myocarditis[d]; pericarditis[d]
Gastrointestinal disorders	Very common	Diarrhoea[d]
	Common	Nausea; vomiting[d,j]
Skin and subcutaneous tissue disorder	Uncommon	Hyperhidrosis; night sweats
	Not known	Erythema multiforme[d]
Musculoskeletal and connective tissue disorders	Very common	Arthralgia; myalgia
	Uncommon	Pain in extremity[e]
Reproductive system and breast disorders	Not known	Heavy menstrual bleeding[i]

System Organ Class	Frequency	Adverse reactions
General disorders and administration site conditions	Very common	Injection site pain; fatigue; chills; pyrexia[f]; injection site swelling
	Common	Injection site redness[h]
	Uncommon	Asthenia; malaise; injection site pruritus
	Not known	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. Injection site redness occurred at a higher frequency (very common) in children 5 to 11 years of age and in immunocompromised participants 5 years of age and older.
i. Most cases appeared to be non-serious and temporary in nature.
j. The frequency category for vomiting was very common in pregnant women 18 years of age and older and in immunocompromised participants 5 to 18 years of age.

Special populations

Infants born to pregnant participants – after 2 doses of Comirnaty
Study C4591015 (Study 9), a Phase 2/3, placebo-controlled study, evaluated a total of 346 pregnant participants who received Comirnaty (n = 173) or placebo (n = 173). Infants (Comirnaty n = 167 or placebo n = 168) were evaluated up to 6 months. No safety concerns were identified that were attributable to maternal vaccination with Comirnaty.

Immunocompromised participants (adults and children)
In study C4591024 (Study 10), a total of 124 immunocompromised participants 2 years of age and older received Comirnaty (see section 5.1).

Safety with concomitant vaccine administration

Concomitant administration with seasonal influenza vaccine
In Study 8, a Phase 3 study, participants 18 to 64 years of age who received Comirnaty coadministered with seasonal inactivated influenza vaccine (SIIV), quadrivalent followed 1 month later by placebo, were compared to participants who received an inactivated influenza vaccine with placebo followed 1 month later by Comirnaty alone (n = 553 to 564 participants in each group).

Concomitant administration with pneumococcal conjugate vaccine
In Study 11 (B7471026), a Phase 3 study, participants 65 years of age and older who received a booster dose of Comirnaty coadministered with 20-valent pneumococcal conjugate vaccine (20vPNC) (n = 187) were compared to participants who received Comirnaty alone (n = 185).

Concomitant administration with an unadjuvanted recombinant protein RSV vaccine or with an unadjuvanted recombinant protein RSV vaccine and a high dose influenza vaccine
In Study 12 (C5481001), a Phase 1/2 study, participants 65 years of age and older who received Comirnaty Original/Omicron BA.4-5 and RSV vaccine coadministered in one arm plus high dose quadrivalent influenza vaccine (QIV) (n = 158) or placebo (n = 157) in the opposite arm were compared to participants who received the individual vaccines given with placebo.

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 via the national reporting system.

4.9 Overdose

There have been reports of higher than recommended doses of Comirnaty in clinical trials and post-authorisation experience. In general, adverse events reported with overdoses have been similar to the known adverse reaction profile of Comirnaty.

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) with Comirnaty and Comirnaty Original/Omicron BA.4-5
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 3.

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

SARS-CoV-2 neutralisation assay	Sampling time point[a]	Vaccine group (as assigned/randomised)				
		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[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])	GMR[d] (95% CI[d])
Omicron BA.4-5 - NT50 (titre)[e]	Pre-vaccination	102	488.3 (361.9, 658.8)	112	248.3 (187.2, 329.5)	-
	1 month	102	2 189.9 (1 742.8, 2 751.7)	113	1 393.6 (1 175.8, 1 651.7)	1.12 (0.92, 1.37)
Reference strain - NT50 (titre)[e]	Pre-vaccination	102	2 904.0 (2 372.6, 3 554.5)	113	1 323.1 (1 055.7, 1 658.2)	-
	1 month	102	8 245.9 (7 108.9, 9 564.9)	113	7 235.1 (6 331.5, 8 267.8)	-

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 × 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 vaccine-naïve participants 12 years of age and older – after a single dose of Comirnaty Omicron XBB.1.5

In an analysis of a subset from Study 13, 302 vaccine-naïve participants 12 years of age and older who were considered to be SARS-CoV-2 positive at baseline and who received 1 dose of Comirnaty Omicron XBB.1.5 were compared to participants who received Comirnaty Omicron XBB.1.5 after at least 3 doses of an mRNA COVID-19 vaccine. The evaluable immunogenicity population who were vaccine-naïve had a median age of 36.0 years and comprised of 62.6% White and 50.7% Hispanic/Latino participants. The evaluable immunogenicity population who were

vaccine experienced (n=296) had a median age of 55 years and comprised of 79.4% White and 18.6% Hispanic/Latino.

Neutralising titres against Omicron XBB.1.5 increased from baseline to 1 month after study vaccination and were greater in participants receiving Comirnaty Omicron XBB.1.5 as a single dose compared with participants who received Comirnaty Omicron XBB.1.5 after at least 3 doses of an mRNA COVID-19 vaccine. Noninferiority was met with respect to the geometric mean ratio (GMR) of Omicron XBB.1.5-neutralising titres, and the difference in seroresponse to the XBB.1.5 strain in vaccine-naïve participants compared to participants who received Comirnaty Omicron XBB.1.5 after at least 3 doses of an mRNA COVID-19 vaccine (Table 4).

Table 4. Geometric mean ratio and difference in percentages of participants with seroresponse – Study 13 vaccine-naïve and subset of vaccine-experienced – evaluable immunogenicity population

		Vaccine group (as assigned)				Group comparison	
		Vaccine-naïve Comirnaty Omicron XBB.1.5 30 mcg		Vaccine-experienced Comirnaty Omicron XBB.1.5 30 mcg		Vaccine-naïve Comirnaty Omicron XBB.1.5 30 mcg / Vaccine-experienced Comirnaty Omicron XBB.1.5 30 mcg	
SARS-CoV-2 neutralisation assay Omicron XBB.1.5 - NT50 (titre)[e]	**Sampling time point[a]**	**n[b]**	**GMT[c] (95% CI[c])**	**n[b]**	**GMT[c] (95% CI[c])**	**GMR[d] (95% CI[d])**	
Geometric mean 50% neutralising titre (GMT)	1 month	299	4 373.4 (3 757.1, 5 090.9)	296	2 915.7 (2 462.4, 3 452.5)	1.93 (1.52, 2.44)[f]	
	Sampling time point[a]	**N[g]**	**n[h] (%) (95% CI[i])**	**N[g]**	**n[h] (%) (95% CI[i])**	**Difference %[j]**	**(95% CI[k])**
Seroresponse rate (%) for 50% neutralising titre	1 month	298	253 (84.9) (80.3, 88.8)	295	218 (73.9) (68.5, 78.8)	7.31	(1.34, 13.28)[l]

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 both the pre−vaccination time point and 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. GMRs and the corresponding 2-sided 95% CIs were calculated by exponentiating the difference in least square means and the corresponding CIs based on a linear regression model with baseline assay results (log scale), age, and vaccine group as covariates.
e. SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (Omicron subvariant XBB.1.5).
f. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67.
g. 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. These values are the denominators for the percentage calculations.
h. n = Number of participants with a seroresponse for the given assay at the given sampling time point.
i. Exact 2-sided CI, based on the Clopper and Pearson method.
j. Difference in proportions, expressed as a percentage.
k. 2-Sided CI, based on the Miettinen and Nurminen method stratified by baseline neutralising titre category (< median, ≥ median) and age group (< median, ≥ median). The median of baseline neutralising titres and median age was calculated based on the pooled data in 2 comparator groups.
l. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is > -10%.

Immunogenicity in participants 12 years of age and older – after a single dose of Comirnaty Omicron JN.1

In an analysis of a subset from Study 13, 212 participants 12 years of age and older who received 1 dose of Comirnaty Omicron JN.1 were compared to 200 participants who received Comirnaty Omicron XBB.1.5 after receiving at least 3 doses of an mRNA COVID-19 vaccine. The evaluable immunogenicity population who received Comirnaty Omicron JN.1 had a median age of 54.5 years and comprised of 69.3% White and 23.1% Hispanic/Latino participants, and 87.3% were positive for SARS-CoV-2 at baseline, and 89.2% had previously received a COVID-19 vaccine.

Neutralising titres and seroresponse against Omicron JN.1 or Omicron XBB.5 in participants receiving Comirnaty Omicron JN.1 or Comirnaty Omicron XBB.1.5 are presented in Table 5.

Table 5. Geometric mean titres and percentage of participants achieving seroresponse – Comirnaty JN.1 or Comirnaty XBB.1.5 – participants 12 years of age and older – evaluable immunogenicity population

		Comirnaty Omicron JN.1 30 mcg		Comirnaty Omicron XBB.1.5 30 mcg	
Geometric mean 50% neutralising titre (GMT)	**Sampling time point[a]**	**n[b]**	**GMT[c] (95% CI[c])**	**n[b]**	**GMT[c] (95% CI[c])**
SARS-CoV-2 neutralisation assay – Omicron JN.1 - NT50 (titre)[d]	Pre-vaccination	211	190.4 (153.6, 235.9)	198	155.5 (126.6, 190.8)
	1 month	212	2203.3 (1855.7, 2616.0)	199	1133.8 (950.7, 1352.2)
SARS-CoV-2 neutralisation assay – Omicron XBB.1.5 – NT50 (titre)[e]	Pre-vaccination	212	290.3 (233.0, 361.6)	200	219.2 (177.5, 270.7)
	1 month	212	2364.4 (1917.4, 2915.6)	200	2848.1 (2341.9, 3463.8)
Seroresponse rate for 50% neutralising titre	**Sampling time point[a]**	**N[f]**	**n[g] (%) (95% CI[h])**	**N[b]**	**n[g] (%) (95% CI[h])**
SARS-CoV-2 neutralisation assay – Omicron JN.1 - NT50 (titre)[d]	1 month	211	149 (70.6) (64.0, 76.7)	197	129 (65.5) (58.4, 72.1)
SARS-CoV-2 neutralisation assay – Omicron XBB.1.5 – NT50 (titre)[e]	1 month	212	128 (60.4) (53.5, 67.0)	200	164 (82.0) (76.0, 87.1)

Abbreviations: 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 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 (Omicron subvariant JN.1).
e. SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (Omicron subvariant XBB.1.5).
f. 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. These values are the denominators for the percentage calculations.
g. n = Number of participants with a seroresponse for the given assay at the given sampling time point.
h. Exact 2-sided CI, based on the Clopper and Pearson method.

Immunogenicity in participants 12 years of age and older – after a single dose of Comirnaty Omicron KP.2

In an analysis of a subset from Study 13, 100 participants 18 years of age and older who received 1 dose of Comirnaty Omicron KP.2 were compared to 194 participants who received 1 dose of Comirnaty Omicron JN.1. The evaluable immunogenicity population who received Comirnaty Omicron KP.2 had a median age of 55.0 years and comprised of 75.0% White and 15.0% Hispanic/Latino participants, 91.0% were positive for SARS-CoV-2 at baseline, and 90.0% had previously received a COVID-19 vaccine.

Neutralising titres and seroresponse against Omicron KP.2 and Omicron JN.1 in participants receiving Comirnaty Omicron KP.2 or Comirnaty Omicron JN.1 are presented in Table 6.

Table 6. Geometric mean titres and percentage of participants achieving seroresponse – Comirnaty KP.2 or Comirnaty JN.1 – participants 18 years of age and older – evaluable immunogenicity population

		Comirnaty Omicron KP.2 30 mcg		Comirnaty Omicron JN.1 30 mcg	
Geometric mean 50% neutralising titre (GMT)	**Sampling time point[a]**	**n[b]**	**GMT[c] (95% CI[c])**	**n[b]**	**GMT[c] (95% CI[c])**
SARS-CoV-2 neutralisation assay – Omicron KP.2 – NT50 (titre)[d]	Pre-vaccination	99	207.6 (150.0, 287.4)	194	78.3 (64.2, 95.6)
	1 month	100	2256.5 (1660.2, 3067.0)	194	873.3 (706.1, 1080.2)
SARS-CoV-2 neutralisation assay – Omicron JN.1 – NT50 (titre)[e]	Pre-vaccination	100	492.5 (359.8, 674.0)	194	185.1 (148.1, 231.4)
	1 month	100	4319.5 (3280.7, 5687.2)	194	2088.6 (1743.9, 2501.5)
Seroresponse rate for 50% neutralising titre	**Sampling time point[a]**	**N[f]**	**n[g] (%) (95% CI[h])**	**N[b]**	**n[g] (%) (95% CI[h])**
SARS-CoV-2 neutralisation assay – Omicron KP.2 – NT50 (titre)[d]	1 month	99	76 (76.8) (67.2, 84.7)	194	130 (67.0) (59.9, 73.6)
SARS-CoV-2 neutralisation assay – Omicron JN.1 – NT50 (titre)[e]	1 month	100	64 (64.0) (53.8, 73.4)	194	137 (70.6) (63.7, 76.9)

Abbreviations: 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 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 (Omicron subvariant KP.2).
e. SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (Omicron subvariant JN.1).
f. 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. These values are the denominators for the percentage calculations.
g. n = Number of participants with a seroresponse for the given assay at the given sampling time point.
h. Exact 2-sided CI, based on the Clopper and Pearson method.

Initially approved Comirnaty vaccine

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 hospitalisation 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/m^2, chronic pulmonary disease, diabetes mellitus, hypertension).

The vaccine efficacy information is presented in Table 7.

Table 7. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of 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 2.214 (17 411)	162 2.222 (17 511)	95.0 (90.0, 97.9)
16 to 64 years	7 1.706 (13 549)	143 1.710 (13 618)	95.1 (89.6, 98.1)
65 years and older	1 0.508 (3 848)	19 0.511 (3 880)	94.7 (66.7, 99.9)
65 to 74 years	1 0.406 (3 074)	14 0.406 (3 095)	92.9 (53.1, 99.8)
75 years and older	0 0.102 (774)	5 0.106 (785)	100.0 (-13.1, 100.0)

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

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

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 8.

Table 8. 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 6.247 (20 712)	850 6.003 (20 713)	91.3 (89.0, 93.2)
16 to 64 years	70 4.859 (15 519)	710 4.654 (15 515)	90.6 (87.9, 92.7)
65 years and older	7 1.233 (4 192)	124 1.202 (4 226)	94.5 (88.3, 97.8)
65 to 74 years	6 0.994 (3 350)	98 0.966 (3 379)	94.1 (86.6, 97.9)
75 years and older	1 0.239 (842)	26 0.237 (847)	96.2 (76.9, 99.9)

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

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

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 9) 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 9. 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 8.439[e] (22 505)	30 8.288[e] (22 435)	96.7 (80.3, 99.9)
7 days after Dose 2[f]	1 6.522[g] (21 649)	21 6.404[g] (21 730)	95.3 (70.9, 99.9)

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, non−invasive 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.

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 10. 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 10. 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

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*			
	COVID-19 mRNA Vaccine 10 mcg/dose N[a]=1 305 Cases n1[b] Surveillance time[c] (n2[d])	**Placebo N[a]=663 Cases n1[b] Surveillance time[c] (n2[d])**	**Vaccine efficacy % (95% CI)**
Children 5 to 11 years of age	3 0.322 (1 273)	16 0.159 (637)	90.7 (67.7, 98.3)

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

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

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

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

c. Total surveillance time in 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.

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 2 703 participants who received the vaccine and 42 cases out of 1 348 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 3 018 who received vaccine and 42 cases in 1 511 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 pre-specified 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 11.

Table 11. 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			
		10 mcg/dose 5 to 11 years N[a]=264	30 mcg/dose 16 to 25 years N[a]=253	5 to 11 years/ 16 to 25 years	
	Time point[b]	GMT[c] (95% CI[c])	GMT[c] (95% CI[c])	GMR[d] (95% CI[d])	Met immunobridging objective[e] (Y/N)
Geometric mean 50% neutralising titre[f] (GMT[c])	1 month after Dose 2	1 197.6 (1 106.1, 1 296.6)	1 146.5 (1 045.5, 1 257.2)	1.04 (0.93, 1.18)	Y
	Time point[b]	**n[g] (%) (95% CI[h])**	**n[g] (%) (95% CI[h])**	**Difference %[i] (95% CI[j])**	**Met immunobridging objective[k] (Y/N)**
Seroresponse rate (%) for 50% neutralising titre[f]	1 month after Dose 2	262 (99.2) (97.3, 99.9)	251 (99.2) (97.2, 99.9)	0.0 (-2.0, 2.2)	Y

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

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

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

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 12. 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 12. 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 0.823 (4 659)	123 0.792 (4 614)	95.3 (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 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 to 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 summarised in Table 13.

Table 13. Summary of geometric mean titres – NT50 – participants without evidence of infection – phase 2/3 – immunogenicity set – 5 to 11 years of age – evaluable immunogenicity population

	Sampling time point[a]		
Assay	1 month after booster dose (n[b]=67) GMT[c] (95% CI[c])	1 month after dose 2 (n[b]=96) GMT[c] (95% CI[c])	1 month after booster dose/ 1 month after dose 2 GMR[d] (95% CI[d])
SARS-CoV-2 neutralisation assay - NT50 (titre)	2 720.9 (2 280.1, 3 247.0)	1 253.9 (1 116.0, 1 408.9)	2.17 (1.76, 2.68)

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

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 × 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).

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 pregnant participants and infants born to pregnant participants – after 2 doses with Comirnaty

Study 9 was a Phase 2/3 multinational, placebo-controlled, observer-blind study that enrolled pregnant participants 18 years of age and older to receive 2 doses of Comirnaty (n = 173) or placebo (n = 173). Pregnant participants received Dose 1 of Comirnaty at 24 to 34 weeks gestation and the majority (90.2%) received the second dose 19 to 23 days after Dose 1.

Descriptive immunogenicity analysis was performed in pregnant participants receiving Comirnaty in Study 9 compared to a comparator subset of nonpregnant participants from Study 2 evaluating the ratio of the neutralising GMT (GMR) 1 month after Dose 2. The evaluable immunogenicity population who received Comirnaty in the pregnant participants group in Study 9 (n = 111) and in nonpregnant

participants in Study 2 (n = 114) had a median age of 30 years (range 18 to 44 years of age) and comprised of 37.8% vs 3.5% with a positive baseline SARS-CoV-2 status, respectively.

Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, the observed SARS-CoV-2 50% neutralising GMT 1 month after Dose 2 was lower in the pregnant participants (Study 9) when compared to nonpregnant female participants (Study 2) (the ratio of the GMT [GMR] was 0.67 (95% CI: 0.50, 0.90).

Among participants with or without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, the model-adjusted GMT 1 month after Dose 2 was similar in the pregnant participants when compared to nonpregnant female participants (the model-adjusted ratio of the GMT [GMR] was 0.95 (95% CI: 0.69, 1.30)). The model-adjusted GMT and GMR were calculated based on a regression model adjusting for age and baseline neutralising titres.

Immunogenicity in immunocompromised participants (adults and children)
Study 10 is a Phase 2b, open-label study (n = 124) that enrolled immunocompromised participants 2 to < 18 years of age receiving immunomodulator therapy or who have undergone solid organ transplant (within the previous 3 months) and are on immunosuppression or who have undergone bone marrow or stem cell transplant at least 6 months prior to enrolment and in immunocompromised participants 18 years of age and older treated for non-small cell lung cancer (NSCLC) or chronic lymphocytic leukaemia (CLL), receiving haemodialysis for secondary to end-stage renal disease, or receiving immunomodulator therapy for an autoimmune inflammatory disorder. Participants received 4 age-appropriate doses of Comirnaty (3 mcg, 10 mcg, or 30 mcg); the first 2 doses separated by 21 days, with the third dose occurring 28 days after the second dose, followed by a fourth dose, 3 to 6 months after Dose 3.

Analysis of immunogenicity data at 1 month after Dose 3 (26 participants 2 to < 5 years of age, 56 participants 5 to < 12 years of age, 11 participants 12 to < 18 years of age, and 4 participants ≥ 18 years of age) and 1 month after Dose 4 (16 participants 2 to < 5 years of age, 31 participants 5 to < 12 years of age, 6 participants 12 to < 18 years of age, and 4 participants ≥ 18 years of age) in the evaluable immunogenicity population without evidence of prior infection demonstrated a vaccine-elicited immune response. GMTs were observed to be substantially higher at 1 month after Dose 3 and further increased at 1 month after Dose 4 and remained high at 6 months after Dose 4 compared to levels observed before study vaccination across age groups and disease subsets.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Comirnaty in one or more subsets of the paediatric population in prevention of COVID-19 (see section 4.2 for information on paediatric use).

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 post-natal 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

The storage and handling conditions printed on the vial or carton labels may differ from those in this product information. In these circumstances, the conditions in the product information should be followed.

Confirm the storage conditions listed for the frozen and refrigerated only vials.

Frozen vials have printed EXP at -90 °C to -60 °C.
Refrigerated only vials have printed EXP at 2 °C to 8 °C.

Unopened frozen vials

Single dose and multidose vials
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.

18 months when stored at -90 °C to -60 °C.
Within the 18-month shelf life the thawed (previously frozen) vials may be stored at 2 °C to 8 °C for up to 10 weeks.

Thawing procedure
Single dose vials
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.

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.

Thawed (previously frozen) vials
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.

Thawed vials can be handled in room light conditions.

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

Unopened refrigerated only vials

Multidose vials
The vaccine will be received and stored at 2 °C to 8 °C (refrigerated only).
12 months when stored at 2 °C to 8 °C.

Opened vials

Once the vaccine vial is punctured it should be used immediately or within 6 hours and kept at 2 °C to 8 °C.

6.4 Special precautions for storage

Frozen vials

Store single dose frozen vials and multidose frozen vials in a freezer at -90 °C to -60 °C.

Refrigerated only vials

Store refrigerated only vials at 2 °C to 8 °C. DO NOT FREEZE.

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

Table 14. Comirnaty JN.1 nature and contents of container

Product presentation	**Contents**	**Container**	**Dose(s) per container (see sections 4.2 and 6.6)**	**Pack sizes**
Comirnaty JN.1 30 micrograms/dose dispersion for injection	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.	Single dose vial (grey cap)	1 dose of 0.3 mL	10 vials
		Multidose (2.25 mL) vial (grey cap)	6 doses of 0.3 mL	10 vials
Comirnaty JN.1 10 micrograms/dose dispersion for injection	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.	Single dose vial (blue cap)	1 dose of 0.3 mL	10 vials
		Multidose (2.25 mL) vial (blue cap)	6 doses of 0.3 mL	10 vials

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The storage and handling conditions printed on the vial or carton labels may differ from those in this product information. In these circumstances, the conditions in the product information should be followed.

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.

Instructions applicable to single dose and multidose vials

- **Verify** that the vial has either:
  - a **grey plastic cap** and the product name is **Comirnaty JN.1 30 micrograms/dose dispersion for injection** (12 years and older), or
  - 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 WHO Product Information for that formulation.

Frozen vials

- 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.
  - Single dose vials: A 10-vial pack of single dose vials may take 2 hours to thaw.
  - Multidose vials: A 10-vial pack of multidose vials may take 6 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).
- Thawed vials can be handled in room light conditions.

Refrigerated only vials

- Unopened vials are stored at 2 °C to 8 °C; not exceeding the printed expiry date (EXP).
- The 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 dispersion may contain white to off-white opaque amorphous particles.
- After mixing, the vaccine should present as a:
  - **Grey cap:** white to off-white dispersion with no particulates visible.
  - **Blue cap:** clear to slightly opalescent dispersion with no particulates visible.
- Do not use the vaccine if particulates or discolouration are present.
- Check whether the vial is a single dose vial or a multidose vial and follow the applicable handling instructions below:
  - Single dose vials
    - Withdraw a single 0.3 mL dose of vaccine.
    - Discard vial and any excess volume.
  - Multidose vials
    - Multidose vials contain 6 doses of 0.3 mL each.
    - Using aseptic technique, cleanse the vial stopper with a single use antiseptic swab.
    - Withdraw 0.3 mL of Comirnaty JN.1.
    - **Low dead-volume syringes and/or needles** should be used in order to extract 6 doses from a single vial. The low dead-volume syringe and needle combination should have a dead-volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial.
    - Each dose must contain 0.3 mL of vaccine.
    - If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
    - Record the appropriate date/time on the multidose vial. Discard any unused vaccine 6 hours after first puncture.

Disposal

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

7. MANUFACTURER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz
Germany
Phone: +49 6131 9084-0
Fax: +49 6131 9084-2121
service@biontech.de

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Comirnaty JN.1 10 micrograms/dose concentrate for dispersion for injection
Comirnaty JN.1 3 micrograms/dose concentrate for dispersion for injection
COVID-19 mRNA Vaccine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Table 1. Comirnaty JN.1 qualitative and quantitative composition

Product presentation	**Container**	**Doses per container (see sections 4.2 and 6.6)**	**Content per dose**
Comirnaty JN.1 10 micrograms/dose concentrate for dispersion for injection	Multidose vial (1.3 mL) (orange cap)	10 doses of 0.2 mL after dilution	One dose (0.2 mL) contains 10 micrograms of bretovameran, a COVID-19 mRNA Vaccine (nucleoside modified, embedded in lipid nanoparticles).
Comirnaty JN.1 3 micrograms/dose concentrate for dispersion for injection	Multidose vial (0.4 mL) (maroon cap)	10 doses of 0.2 mL after dilution	One dose (0.2 mL) contains 3 micrograms of bretovameran, a COVID-19 mRNA Vaccine (nucleoside modified, embedded in lipid nanoparticles).
	Multidose vial (0.48 mL) (yellow cap)	3 doses of 0.3 mL after dilution	One dose (0.3 mL) contains 3 micrograms of bretovameran, a COVID-19 mRNA Vaccine (nucleoside modified, embedded in lipid nanoparticles).

Bretovameran is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 (Omicron JN.1).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for dispersion for injection (sterile concentrate).

Comirnaty JN.1 10 micrograms/dose concentrate for dispersion for injection is a white to off-white dispersion (pH: 6.9 - 7.9).

Comirnaty JN.1 3 micrograms/dose concentrate for dispersion for injection:

Container	**Appearance**
Multidose vial (0.4 mL) (maroon cap)	The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9).
Multidose vial (0.48 mL) (yellow cap)	The vaccine is a clear to slightly opalescent dispersion (pH: 6.9 - 7.9).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Comirnaty JN.1 concentrate for dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in infants and children aged 6 months to 11 years.

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

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 concentrate for dispersion for injection is administered intramuscularly after dilution as a single dose of 0.2 mL for children 5 to 11 years of age 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 JN.1 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Infants and children 6 months to 4 years of age without history of completion of a COVID-19 primary course or prior SARS-CoV-2 infection
Comirnaty JN.1 3 micrograms/dose concentrate for dispersion for injection is administered intramuscularly after dilution as a primary course of 3 doses. It is recommended to administer the second dose 3 weeks after the first dose followed by a third dose administered at least 8 weeks after the second dose (see sections 4.4 and 5.1).

If a child turns 5 years old between their doses in the primary course, he/she should complete the primary course at the same 3 micrograms dose level.

Infants and children 6 months to 4 years of age with history of completion of a COVID-19 primary course or prior SARS-CoV-2 infection
Comirnaty JN.1 3 micrograms/dose concentrate for dispersion for injection is administered intramuscularly after dilution as a single dose for infants and children 6 months to 4 years of age.

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

Severely immunocompromised individuals
Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations (see section 4.4).

Interchangeability
The Comirnaty JN.1 3 micrograms/dose primary course may consist of either Comirnaty, Comirnaty Original/Omicron BA.4-5, Comirnaty Omicron XBB.1.5 or Comirnaty JN.1 (or a combination) but not exceeding the total number of doses required as primary course. The primary course should only be administered once.

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

Paediatric population
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 concentrate for dispersion for injection should be administered intramuscularly after dilution (see section 6.6).

Orange cap (10-dose vial) or maroon cap (10-dose vial)
After dilution, vials with an **orange cap** or **maroon cap** of Comirnaty JN.1 contain **10 doses of 0.2 mL** of vaccine. In order to extract 10 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 10 doses from a single vial. Irrespective of the type of syringe and needle:

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

Yellow cap (3-dose vial)
After dilution, vials with a **yellow cap** of Comirnaty JN.1 contain **3 doses of 0.3 mL** of vaccine. Standard syringes and needles can be used to extract 3 doses from a single vial. Irrespective of the type of syringe and needle:

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

In infants from 6 to less than 12 months of age, the recommended injection site is the anterolateral aspect of the thigh. In individuals 1 to 4 years of age, the recommended injection site is the anterolateral aspect of the thigh or the deltoid muscle. In individuals 5 years of age and older 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.

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
Safety and immunogenicity have been assessed in a limited number of immunocompromised individuals, including those receiving immunosuppressant therapy (see sections 4.8 and 5.1). 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, there are limited clinical study data (less than 300 pregnancy outcomes) from the use of Comirnaty in pregnant participants. 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 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 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 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).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of safety profile

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

Initially approved Comirnaty vaccine
Infants 6 to 23 months of age – after 3 doses
In an analysis of Study 3 (Phase 2/3), 2 176 infants (1 458 initially approved Comirnaty 3 mcg and 718 placebo) were 6 to 23 months of age. Based on data in the blinded placebo-controlled follow-up period up to the cut-off date of 28 February 2023, 720 infants 6 to 23 months of age who received a 3-dose primary course (483 Comirnaty 3 mcg and 237 placebo) have been followed for a median of 1.7 months after the third dose.

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

Children 2 to 4 years of age – after 3 doses
In an analysis of Study 3 (Phase 2/3), 3 541 children (2 368 Comirnaty 3 mcg and 1 173 placebo) were 2 to 4 years of age. Based on data in the blinded placebo-controlled follow-up period up to the cut-off date of 28 February 2023, 1 268 children 2 to 4 years of age who received a 3-dose primary course

(863 Comirnaty 3 mcg and 405 placebo) have been followed a median of 2.2 months after the third dose.

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

Children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after 2 doses
In Study 3, a total of 3 109 children 5 to 11 years of age received at least 1 dose of the initially approved Comirnaty vaccine and a total of 1 538 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, 2 206 (1 481 Comirnaty 10 mcg and 725 placebo) children have been followed for ≥ 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 (≥ 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 2 408 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, 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.

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 22 026 participants 16 years of age or older received at least 1 dose of Comirnaty 30 mcg 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.

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 ≥ 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.

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

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

Omicron-adapted Comirnaty
Infants 6 to 23 months of age – after the booster (fourth dose)
In 2 groups from Study 6 (Phase 3, Groups 2 and 3), 160 participants (Group 2: 92, Group 3: 68) 6 to 23 months of age who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (1.5/1.5 mcg) 2.1 to 8.6 months after receiving Dose 3 for Group 2 and 3.8 to 12.5 months after receiving Dose 3 for Group 3. Participants who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 had a median follow-up time of 4.4 months for Group 2 and had a median follow-up time of 6.4 months for Group 3.

The overall safety profile for the Comirnaty Original/Omicron BA.4-5 booster (fourth dose) was similar to that seen after 3 doses. The most frequent adverse reaction in participants 6 to 23 months of age was irritability (> 30%), decreased appetite (> 20%), drowsiness, tenderness at the injection site and fever (> 10%).

Children 2 to 4 years of age – after the booster (fourth dose)
In 2 groups from Study 6 (Phase 3, Groups 2 and 3), 1 207 participants (Group 2: 218, Group 3: 989) 2 to 4 years of age who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (1.5/1.5 mcg) 2.1 to 8.6 months after receiving Dose 3 for Group 2 and 2.8 to 17.5 months after receiving Dose 3 for Group 3. Participants who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 had a median follow-up time of 4.6 months for Group 2 and had a median follow-up time of 6.3 months for Group 3.

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

Children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after the booster (fourth dose)
In a subset from Study 6 (Phase 3), 113 participants 5 to 11 years of age who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (5/5 mcg) 2.6 to 8.5 months after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 had a median follow-up time of 6.3 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 myalgia (> 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%), myalgia (> 20%), chills (> 10%), and arthralgia (> 10%).

Participants 12 years of age and older – after a booster dose of Comirnaty Omicron XBB.1.5 (fourth dose or more)
In a subset from Study 13 (Phase 2/3), 412 participants 12 years of age and older, who had received at least 3 doses of an authorised mRNA COVID-19 vaccine, received a booster (fourth dose or more) of Comirnaty Omicron XBB.1.5 2.0 to 24.1 months after receiving Dose 3. Participants who received a booster (fourth dose or more) of Comirnaty XBB.1.5 had a median follow-up time of 6.3 months.

The safety profile of Comirnaty Omicron XBB.1.5 was similar to the overall Comirnaty safety profile.

Participants 12 years of age and older – after a single dose of Comirnaty Omicron XBB.1.5
In a subset from Study 13 (Phase 2/3), 311 participants 12 years of age and older who were considered to be baseline SARS-CoV-2 positive and COVID-19 vaccine-naïve, received 1 dose of Comirnaty Omicron XBB.1.5. Participants had a median follow-up time of 6.4 months.

The safety profile of Comirnaty Omicron XBB.1.5 was similar to the overall Comirnaty safety profile. The most frequent adverse reactions in participants were injection site pain (> 50%), fatigue (> 30%), headache (> 20%), myalgia, diarrhoea, arthralgia, chills and injection site swelling (> 10%).

Participants 12 years of age and older – after a single dose of Comirnaty Omicron JN.1
In a subset from Study 13 (Phase 2/3), 216 participants 12 years of age and older received 1 dose of Comirnaty Omicron JN.1 and had a median follow-up time of 6.3 months.

The safety profile of Comirnaty Omicron JN.1 was similar to the overall Comirnaty safety profile. The most frequent adverse reactions in participants were injection site pain (> 60%), fatigue (>30%), headache (>20%), myalgia, chills and injection site swelling (>10%).

Participants 18 years of age and older – after a single dose of Comirnaty Omicron KP.2
In a subset from Study 13 (Phase 2/3), 102 participants 18 years of age and older received 1 dose of Comirnaty Omicron KP.2 and had a median follow-up time of 6.3 months.

The safety profile of Comirnaty Omicron KP.2 was similar to the overall Comirnaty safety profile. The most frequent adverse reactions in participants were injection site pain (> 50%), fatigue (>40%), headache and myalgia (>20%).

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

Adverse reactions observed during clinical studies and post-authorisation experience 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 2. Adverse reactions from Comirnaty and Comirnaty Original/Omicron BA.4-5 clinical trials and Comirnaty post-authorisation experience in individuals 6 months of age and older

System Organ Class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Common	Lymphadenopathy[a]
Immune system disorders	Uncommon	Hypersensitivity reactions (e.g. rash[i], pruritus, urticaria[b], angioedema[b])
	Not known	Anaphylaxis
Metabolism and nutrition disorders	Uncommon	Decreased appetite[j]
Psychiatric disorders	Very common	Irritability[k]
	Uncommon	Insomnia
Nervous system disorders	Very common	Headache; drowsiness[k]
	Uncommon	Dizziness[d]; lethargy
	Rare	Acute peripheral facial paralysis[c]
	Not known	Paraesthesia[d]; hypoaesthesia[d]
Cardiac disorders	Very rare	Myocarditis[d]; pericarditis[d]
Gastrointestinal disorders	Very common	Diarrhoea[d]
	Common	Nausea; vomiting[d,m]
Skin and subcutaneous tissue disorder	Uncommon	Hyperhidrosis; night sweats
	Not known	Erythema multiforme[d]
Musculoskeletal and connective tissue disorders	Very common	Arthralgia; myalgia
	Uncommon	Pain in extremity[e]
Reproductive system and breast disorders	Not known	Heavy menstrual bleeding[l]
General disorders and administration site conditions	Very common	Injection site pain; injection site tenderness[k]; fatigue; chills; pyrexia[f]; injection site swelling
	Common	Injection site redness[h]
	Uncommon	Asthenia; malaise; injection site pruritus
	Not known	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 (participants 5 years and older) and angioedema (participants 6 months and older) was rare.
c. Through the clinical trial safety follow-up period to 14 November 2020, acute peripheral facial paralysis (or palsy) was reported by four participants in the COVID-19 mRNA Vaccine group. Onset was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.
d. Adverse reaction determined post-authorisation.
e. Refers to vaccinated arm.
f. A higher frequency of pyrexia was observed after the second dose compared to the first dose.

g. Facial swelling in vaccine recipients with a history of injection of dermatological fillers has been reported in the post-marketing phase.
h. Injection site redness occurred at a higher frequency (very common) in participants 6 months to 11 years of age and in immunocompromised participants 2 years of age and older.
i. The frequency category for rash was common in participants 6 to 23 months of age.
j. The frequency category for decreased appetite was very common in participants 6 to 23 months of age.
k. Irritability, injection site tenderness, and drowsiness pertain to participants 6 to 23 months of age.
l. Most cases appeared to be non-serious and temporary in nature.
m. The frequency category for vomiting was very common in pregnant women 18 years of age and older and in immunocompromised participants 2 to 18 years of age.

Special populations

Infants born to pregnant participants – after 2 doses of Comirnaty
Study C4591015 (Study 9), a Phase 2/3, placebo-controlled study, evaluated a total of 346 pregnant participants who received Comirnaty (n = 173) or placebo (n = 173). Infants (Comirnaty n = 167 or placebo n = 168) were evaluated up to 6 months. No safety concerns were identified that were attributable to maternal vaccination with Comirnaty.

Immunocompromised participants (adults and children)
In study C4591024 (Study 10), a total of 124 immunocompromised participants 2 years of age and older received Comirnaty (see section 5.1).

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 via the national reporting system.

4.9 Overdose

There have been reports of higher than recommended doses of Comirnaty in clinical trials and post-authorisation experience. In general, adverse events reported with overdoses have been similar to the known adverse reaction profile of Comirnaty.

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 infants and children 6 months to 4 years of age – after the booster (fourth dose) with Comirnaty and Comirnaty Original/Omicron BA.4-5
In an analysis of a subset from Study 6, 310 participants 6 months to 4 years of age received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (1.5/1.5 mcg) after receiving 3 prior doses of Comirnaty 3 micrograms dose concentrate for dispersion. Results include immunogenicity data from a comparator subset of participants 6 months to 4 years of age in Study 3 who received 3 doses of Comirnaty 3 micrograms dose concentrate for dispersion.

Analyses of NT50 against Omicron BA.4-5 and against reference strain among participants 6 months to 5 years of age who received Comirnaty (Bivalent BA.4-5) as a booster dose in Study 6 compared to a subset of participants from Study 3 who received 3 doses of Comirnaty demonstrated superiority of anti-Omicron BA.4-5 response based on GMR and noninferiority based on difference in seroresponse rates, and noninferiority of anti-reference strain immune response based on GMR and difference in seroresponse rates (Table 3).

Table 3. Substudy B group 2 – Geometric mean ratios and difference in percentages of participants with seroresponse (1 month after dose 4 study 6/1 month after dose 3 study 3) - participants with or without evidence of infection - 6 months to 4 years of age - evaluable immunogenicity population

Geometric mean ratios (1 month after dose 4 study 6/1 month after dose 3 study 3)					
	Comirnaty (Bivalent BA.4-5) (3 mcg) Study 6		Comirnaty (3 mcg) Subset of Study 3		Comirnaty (Bivalent BA.4-5) (3 mcg) / Comirnaty (3 mcg)
Assay[f]	n[a]	GMT[b] (95% CI[b])	n[a]	GMT[b] (95% CI[b])	GMR[c] (95% CI)[c]
SARS-CoV-2 neutralisation assay - Omicron BA.4-5 - NT50 (titre)	223	1 839.3 (1 630.5, 2 074.9)	238	941.0 (838.1,1 058.2)	1.95 (1.65, 2.31)[d]
SARS-CoV-2 neutralisation assay – reference strain - NT50 (titre)	223	6 636.3 (6 017.5, 7 318.8)	238	7 305.4 (6 645.5, 8 030.7)	0.91 (0.79, 1.04)[e]

Difference in percentages of participants with seroresponse (1 month after dose 4 study 6/1 month after dose 3 study 3)					
Assay[f]	**Comirnaty (Bivalent BA.4-5) (3 mcg) Study 6**		**Comirnaty (3 mcg) Subset of Study 3**		**Difference**
	N[g]	**n[h] (%) (95% CI[i])**	**N[g]**	**n[h] (%) (95% CI[i])**	**%[j] (95% CI[k])**
SARS-CoV-2 neutralisation assay - Omicron BA.4-5 - NT50 (titre)	223	149 (66.8) (60.2, 73.0)	238	120 (50.4) (43.9, 56.9)	19.99 (11.61, 28.36)[l]
SARS-CoV-2 neutralisation assay – reference strain – NT50 (titre)	223	110 (49.3) (42.6, 56.1)	238	141 (59.2) (52.7, 65.5)	-0.15 (-7.79, 7.48)[m]

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

Note: Seroresponse is defined as achieving a ≥ 4-fold rise from baseline (before the first dose of study vaccination). If the baseline measurement is below the LLOQ, the post-vaccination measure of ≥ 4 × LLOQ is considered 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 CIs were calculated by exponentiating the LSMeans 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, age group (for ≥ 6 Months to < 5 Years only) and vaccine group as covariates. Assay results below the LLOQ were set to 0.5 × LLOQ.
c. GMRs and 2-sided CIs were calculated by exponentiating the difference of LSMeans for the assay and the corresponding CIs based on the same regression model as stated above.
d. Superiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 1.
e. 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.
f. 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).
g. 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. These values are the denominators for the percentage calculations.
h. n = Number of participants with seroresponse for the given assay at the given sampling time point.
i. Exact 2-sided CI based on the Clopper and Pearson method.
j. Adjusted difference in proportions, based on the Miettinen and Nurminen stratified by baseline neutralising titre category (< median, ≥ median), expressed as a percentage Comirnaty (Bivalent BA.4-5) [3 mcg] – Comirnaty [3 mcg]. The median of baseline neutralising titres was calculated based on the pooled data in 2 comparator groups.
k. 2-sided CI based on the Miettinen and Nurminen method for the difference in proportions stratified by baseline neutralising titre category (< median, ≥ median), expressed as a percentage.
l. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is > -5%.
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%.

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 4.

Table 4. 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[a]	Vaccine group (as assigned/randomised)				
		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[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])	GMR[d] (95% CI[d])
Omicron BA.4-5 - NT50 (titre)[e]	Pre-vaccination	102	488.3 (361.9, 658.8)	112	248.3 (187.2, 329.5)	-
	1 month	102	2 189.9 (1 742.8, 2 751.7)	113	1 393.6 (1 175.8, 1 651.7)	1.12 (0.92, 1.37)
Reference strain - NT50 (titre)[e]	Pre-vaccination	102	2 904.0 (2 372.6, 3 554.5)	113	1 323.1 (1 055.7, 1 658.2)	-
	1 month	102	8 245.9 (7 108.9, 9 564.9)	113	7 235.1 (6 331.5, 8 267.8)	-

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 × 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 vaccine-naïve participants 12 years of age and older – after a single dose of Comirnaty Omicron XBB.1.5

In an analysis of a subset from Study 13, 302 vaccine-naïve participants 12 years of age and older who were considered to be SARS-CoV-2 positive at baseline and who received 1 dose of Comirnaty Omicron XBB.1.5 were compared to participants who received Comirnaty Omicron XBB.1.5 after at least 3 doses of an mRNA COVID-19 vaccine. The evaluable immunogenicity population who were vaccine-naïve had a median age of 36.0 years and comprised of 62.6% White and 50.7% Hispanic/Latino participants. The evaluable immunogenicity population who were vaccine experienced (n=296) had a median age of 55 years and comprised of 79.4% White and 18.6% Hispanic/Latino.

Neutralising titres against Omicron XBB.1.5 increased from baseline to 1 month after study vaccination and were greater in participants receiving Comirnaty Omicron XBB.1.5 as a single dose

compared with participants who received Comirnaty Omicron XBB.1.5 after at least 3 doses of an mRNA COVID-19 vaccine. Noninferiority was met with respect to the geometric mean ratio (GMR) of Omicron XBB.1.5-neutralising titres, and the difference in seroresponse to the XBB.1.5 strain in vaccine-naïve participants compared to participants who received Comirnaty Omicron XBB.1.5 after at least 3 doses of an mRNA COVID-19 vaccine (Table 5).

Table 5. Geometric mean ratio and difference in percentages of participants with seroresponse – Study 13 vaccine-naïve and subset of vaccine-experienced – evaluable immunogenicity population

		Vaccine group (as assigned)				Group comparison	
		Vaccine-naïve Comirnaty Omicron XBB.1.5 30 mcg		Vaccine-experienced Comirnaty Omicron XBB.1.5 30 mcg		Vaccine-naïve Comirnaty Omicron XBB.1.5 30 mcg / Vaccine-experienced Comirnaty Omicron XBB.1.5 30 mcg	
SARS-CoV-2 neutralisation assay Omicron XBB.1.5 - NT50 (titre)[e]	**Sampling time point[a]**	**n[b]**	**GMT[c] (95% CI[c])**	**n[b]**	**GMT[c] (95% CI[c])**	**GMR[d] (95% CI[d])**	
Geometric mean 50% neutralising titre (GMT)	1 month	299	4 373.4 (3 757.1, 5 090.9)	296	2 915.7 (2 462.4, 3 452.5)	1.93 (1.52, 2.44)[f]	
	Sampling time point[a]	**N[g]**	**n[h] (%) (95% CI[i])**	**N[g]**	**n[h] (%) (95% CI[i])**	**Difference %[j]**	**(95% CI[k])**
Seroresponse rate (%) for 50% neutralising titre	1 month	298	253 (84.9) (80.3, 88.8)	295	218 (73.9) (68.5, 78.8)	7.31	(1.34, 13.28)[l]

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 both the pre−vaccination time point and 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. GMRs and the corresponding 2-sided 95% CIs were calculated by exponentiating the difference in least square means and the corresponding CIs based on a linear regression model with baseline assay results (log scale), age, and vaccine group as covariates.
e. SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (Omicron subvariant XBB.1.5).
f. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67.
g. 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. These values are the denominators for the percentage calculations.
h. n = Number of participants with a seroresponse for the given assay at the given sampling time point.
i. Exact 2-sided CI, based on the Clopper and Pearson method.
j. Difference in proportions, expressed as a percentage.
k. 2-Sided CI, based on the Miettinen and Nurminen method stratified by baseline neutralising titre category (< median, ≥ median) and age group (< median, ≥ median). The median of baseline neutralising titres and median age was calculated based on the pooled data in 2 comparator groups.
l. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is > -10%.

Immunogenicity in participants 12 years of age and older – after a single dose of Comirnaty Omicron JN.1

In an analysis of a subset from Study 13, 212 participants 12 years of age and older who received 1 dose of Comirnaty Omicron JN.1 were compared to 200 participants who received Comirnaty Omicron XBB.1.5 after receiving at least 3 doses of an mRNA COVID-19 vaccine. The evaluable immunogenicity population who received Comirnaty Omicron JN.1 had a median age of 54.5 years and comprised of 69.3% White and 23.1% Hispanic/Latino participants, and 87.3% were positive for SARS-CoV-2 at baseline, and 89.2% had previously received a COVID-19 vaccine.

Neutralising titres and seroresponse against Omicron JN.1 or Omicron XBB.5 in participants receiving Comirnaty Omicron JN.1 or Comirnaty Omicron XBB.1.5 are presented in Table 6.

Table 6. Geometric mean titres and percentage of participants achieving seroresponse – Comirnaty JN.1 or Comirnaty XBB.1.5 – participants 12 years of age and older – evaluable immunogenicity population

		Comirnaty Omicron JN.1 30 mcg		Comirnaty Omicron XBB.1.5 30 mcg	
Geometric mean 50% neutralising titre (GMT)	**Sampling time point[a]**	**n[b]**	**GMT[c] (95% CI[c])**	**n[b]**	**GMT[c] (95% CI[c])**
SARS-CoV-2 neutralisation assay – Omicron JN.1 - NT50 (titre)[d]	Pre-vaccination	211	190.4 (153.6, 235.9)	198	155.5 (126.6, 190.8)
	1 month	212	2203.3 (1855.7, 2616.0)	199	1133.8 (950.7, 1352.2)
SARS-CoV-2 neutralisation assay – Omicron XBB.1.5 – NT50 (titre)[e]	Pre-vaccination	212	290.3 (233.0, 361.6)	200	219.2 (177.5, 270.7)
	1 month	212	2364.4 (1917.4, 2915.6)	200	2848.1 (2341.9, 3463.8)
Seroresponse rate for 50% neutralising titre	**Sampling time point[a]**	**N[f]**	**n[g] (%) (95% CI[h])**	**N[b]**	**n[g] (%) (95% CI[h])**
SARS-CoV-2 neutralisation assay – Omicron JN.1 - NT50 (titre)[d]	1 month	211	149 (70.6) (64.0, 76.7)	197	129 (65.5) (58.4, 72.1)
SARS-CoV-2 neutralisation assay – Omicron XBB.1.5 – NT50 (titre)[e]	1 month	212	128 (60.4) (53.5, 67.0)	200	164 (82.0) (76.0, 87.1)

Abbreviations: 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 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 (Omicron subvariant JN.1).
e. SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (Omicron subvariant XBB.1.5).
f. 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. These values are the denominators for the percentage calculations.
g. n = Number of participants with a seroresponse for the given assay at the given sampling time point.
h. Exact 2-sided CI, based on the Clopper and Pearson method.

Immunogenicity in participants 18 years of age and older – after a single dose of Comirnaty Omicron KP.2

In an analysis of a subset from Study 13, 100 participants 18 years of age and older who received 1 dose of Comirnaty Omicron KP.2 were compared to 194 participants who received 1 dose of Comirnaty Omicron JN.1. The evaluable immunogenicity population who received Comirnaty Omicron KP.2 had a median age of 55.0 years and comprised of 75.0% White and 15.0% Hispanic/Latino participants, 91.0% were positive for SARS-CoV-2 at baseline, and 90.0% had previously received a COVID-19 vaccine.

Neutralising titres and seroresponse against Omicron KP.2 and Omicron JN.1 in participants receiving Comirnaty Omicron KP.2 or Comirnaty Omicron JN.1 are presented in Table 7.

Table 7. Geometric mean titres and percentage of participants achieving seroresponse – Comirnaty KP.2 or Comirnaty JN.1 – participants 18 years of age and older – evaluable immunogenicity population

		Comirnaty Omicron KP.2 30 mcg		Comirnaty Omicron JN.1 30 mcg	
Geometric mean 50% neutralising titre (GMT)	**Sampling time point[a]**	**n[b]**	**GMT[c] (95% CI[c])**	**n[b]**	**GMT[c] (95% CI[c])**
SARS-CoV-2 neutralisation assay – Omicron KP.2 – NT50 (titre)[d]	Pre-vaccination	99	207.6 (150.0, 287.4)	194	78.3 (64.2, 95.6)
	1 month	100	2256.5 (1660.2, 3067.0)	194	873.3 (706.1, 1080.2)
SARS-CoV-2 neutralisation assay – Omicron JN.1 – NT50 (titre)[e]	Pre-vaccination	100	492.5 (359.8, 674.0)	194	185.1 (148.1, 231.4)
	1 month	100	4319.5 (3280.7, 5687.2)	194	2088.6 (1743.9, 2501.5)
Seroresponse rate for 50% neutralising titre	**Sampling time point[a]**	**N[f]**	**n[g] (%) (95% CI[h])**	**N[b]**	**n[g] (%) (95% CI[h])**
SARS-CoV-2 neutralisation assay – Omicron KP.2 – NT50 (titre)[d]	1 month	99	76 (76.8) (67.2, 84.7)	194	130 (67.0) (59.9, 73.6)
SARS-CoV-2 neutralisation assay – Omicron JN.1 – NT50 (titre)[e]	1 month	100	64 (64.0) (53.8, 73.4)	194	137 (70.6) (63.7, 76.9)

Abbreviations: 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 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 (Omicron subvariant KP.2).
e. SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (Omicron subvariant JN.1).
f. 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. These values are the denominators for the percentage calculations.
g. n = Number of participants with a seroresponse for the given assay at the given sampling time point.
h. Exact 2-sided CI, based on the Clopper and Pearson method.

Comirnaty

Study 2 is a multicentre, multinational, Phase 1/2/3 randomised, placebo-controlled, observer-blind dose-finding, vaccine candidate selection and efficacy study in participants 12 years of age and older. Randomisation was stratified by age: 12 to 15 years of age, 16 to 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥ 56-year stratum. The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19. Participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalisation 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/m^2, chronic pulmonary disease, diabetes mellitus, hypertension).

The vaccine efficacy information is presented in Table 8.

Table 8. 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 2.214 (17 411)	162 2.222 (17 511)	95.0 (90.0, 97.9)
16 to 64 years	7 1.706 (13 549)	143 1.710 (13 618)	95.1 (89.6, 98.1)
65 years and older	1 0.508 (3 848)	19 0.511 (3 880)	94.7 (66.7, 99.9)
65 to 74 years	1 0.406 (3 074)	14 0.406 (3 095)	92.9 (53.1, 99.8)
75 years and older	0 0.102 (774)	5 0.106 (785)	100.0 (-13.1, 100.0)

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

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

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 9.

Table 9. 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 6.247 (20 712)	850 6.003 (20 713)	91.3 (89.0, 93.2)
16 to 64 years	70 4.859 (15 519)	710 4.654 (15 515)	90.6 (87.9, 92.7)
65 years and older	7 1.233 (4 192)	124 1.202 (4 226)	94.5 (88.3, 97.8)
65 to 74 years	6 0.994 (3 350)	98 0.966 (3 379)	94.1 (86.6, 97.9)
75 years and older	1 0.239 (842)	26 0.237 (847)	96.2 (76.9, 99.9)

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

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

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 10) as the COVID-19 case counts in participants without prior SARS-CoV-2 infection were the same as those in participants with or without prior SARS-CoV-2 infection in both the COVID-19 mRNA Vaccine and placebo groups.

Table 10. Vaccine efficacy – First severe COVID-19 occurrence in participants with or without prior SARS-CoV-2 infection based on 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 8.439[e] (22 505)	30 8.288[e] (22 435)	96.7 (80.3, 99.9)
7 days after Dose 2[f]	1 6.522[g] (21 649)	21 6.404[g] (21 730)	95.3 (70.9, 99.9)

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, non−invasive 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.

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 11. 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 11. 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

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*			
	COVID-19 mRNA Vaccine 10 mcg/dose N[a]=1 305 Cases n1[b] Surveillance time[c] (n2[d])	**Placebo N[a]=663 Cases n1[b] Surveillance time[c] (n2[d])**	**Vaccine efficacy % (95% CI)**
Children 5 to 11 years of age	3 0.322 (1 273)	16 0.159 (637)	90.7 (67.7, 98.3)

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

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

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

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

c. Total surveillance time in 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.

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 2 703 participants who received the vaccine and 42 cases out of 1 348 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 3 018 who received vaccine and 42 cases in 1 511 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 pre-specified 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 12.

Table 12. 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			
		10 mcg/dose 5 to 11 years N[a]=264	30 mcg/dose 16 to 25 years N[a]=253	5 to 11 years/ 16 to 25 years	
	Time point[b]	GMT[c] (95% CI[c])	GMT[c] (95% CI[c])	GMR[d] (95% CI[d])	Met immunobridging objective[e] (Y/N)
Geometric mean 50% neutralising titre[f] (GMT[c])	1 month after Dose 2	1 197.6 (1 106.1, 1 296.6)	1 146.5 (1 045.5, 1 257.2)	1.04 (0.93, 1.18)	Y
	Time point[b]	**n[g] (%) (95% CI[h])**	**n[g] (%) (95% CI[h])**	**Difference %[i] (95% CI[j])**	**Met immunobridging objective[k] (Y/N)**
Seroresponse rate (%) for 50% neutralising titre[f]	1 month after Dose 2	262 (99.2) (97.3, 99.9)	251 (99.2) (97.2, 99.9)	0.0 (-2.0, 2.2)	Y

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

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

Note: Seroresponse is defined as achieving a ≥ 4-fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a post-vaccination assay result ≥ 4 × 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 × 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 ≥ 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 to 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 summarised in Table 13.

Table 13. Summary of geometric mean titres – NT50 – participants without evidence of infection – phase 2/3 – immunogenicity set – 5 to 11 years of age – evaluable immunogenicity population

	Sampling time point[a]		
Assay	**1 month after booster dose (n[b]=67) GMT[c] (95% CI[c])**	**1 month after dose 2 (n[b]=96) GMT[c] (95% CI[c])**	**1 month after booster dose/ 1 month after dose 2 GMR[d] (95% CI[d])**
SARS-CoV-2 neutralisation assay - NT50 (titre)	2 720.9 (2 280.1, 3 247.0)	1 253.9 (1 116.0, 1 408.9)	2.17 (1.76, 2.68)

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

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 × 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).

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

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

The vaccine efficacy results after Dose 3 in participants 6 months to 4 years of age are presented in Table 14.

Table 14. Vaccine efficacy – first COVID-19 occurrence from 7 days after Dose 3 – blinded follow-up period – participants without evidence of infection prior to 7 days after Dose 3 – phase 2/3 – 6 months to 4 years of age – evaluable efficacy (3-dose) population

First COVID-19 occurrence from 7 days after Dose 3 in participants without evidence of prior SARS-CoV-2 infection*			
Subgroup	**COVID-19 mRNA Vaccine 3 mcg/Dose N[a]=873 Cases n1[b] Surveillance Time[c] (n2[d])**	**Placebo N[a]=381 Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI[e])**
6 months to 4 years[e]	13 0.124 (794)	21 0.054 (351)	73.2 (43.8, 87.6)
2 to 4 years	9 0.081 (498)	13 0.033 (204)	71.8 (28.6, 89.4)
6 months to 23 months	4 0.042 (296)	8 0.020 (147)	75.8 (9.7, 94.7)

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

* Participants who had no serological or virological evidence (prior to 7 days after receipt of Dose 3) of past SARS-CoV-2 infection (i.e. negative N-binding antibody [serum] result at Dose 1, 1 month post-Dose 2 (if available), Dose 3 (if available) visits, SARS-CoV-2 not detected by NAAT [nasal swab] at Dose 1, Dose 2, and Dose 3 study visits, and a negative NAAT [nasal swab] result at any unscheduled visit prior to 7 days after receipt of Dose 3) and had no medical history of COVID-19 were included in the analysis.

a. N = number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 3 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Two-sided 95% confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.

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

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

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

SARS-CoV-2 50% neutralising antibody titres (NT50) were compared between an immunogenicity subset of Phase 2/3 participants 6 to 23 months of age and 2 to 4 years of age from Study 3 at 1 month after the 3-dose primary course and a randomly selected subset from Study 2 Phase 2/3 participants 16 to 25 years of age at 1 month after the 2-dose primary course, using a microneutralisation assay against the reference strain (USA_WA1/2020).

The primary immunobridging analyses compared the geometric mean titres (using a geometric mean ratio [GMR]) and the seroresponse (defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from before Dose 1) rates in the evaluable immunogenicity population of participants without evidence of prior SARS-CoV-2 infection up to 1 month after Dose 3 in participants 6 to 23 months of age and 2 to 4 years of age and up to 1 month after Dose 2 in participants 16 to 25 years of age. The

pre-specified immunobridging criteria were met for both the GMR and the seroresponse difference for both age groups (Table 15).

Table 15. SARS-CoV-2 GMTs (NT50) and difference in percentages of participants with seroresponse at 1 month after vaccination course – immunobridging subset - participants 6 months to 4 years of age (Study 3) 1 month after Dose 3 and participants 16 to 25 years of age (Study 2) 1 month after Dose 2 – without evidence of SARS-CoV-2 infection – evaluable immunogenicity population

SARS-CoV-2 GMTs (NT50) at 1 month after vaccination course							
SARS-CoV-2 neutralisation assay - NT50 (titre)[e]							
Age	**N[a]**	**GMT[b] (95% CI[b]) (1 month after Dose 3)**	**Age**	**N[a]**	**GMT[b] (95% CI[b]) (1 month after Dose 2)**	**Age**	**GMR[c,d] (95% CI)**
2 to 4 years	143	1 535.2 (1 388.2, 1 697.8)	16 to 25 years of age	170	1 180.0 (1 066.6, 1 305.4)	2 to 4 years/16 to 25 years of age	1.30 (1.13, 1.50)
6 to 23 months	82	1 406.5 (1 211.3, 1 633.1)	16 to 25 years of age	170	1 180.0 (1 066.6, 1 305.4)	6 to 23 months years/16 to 25 years of age	1.19 (1.00, 1.42)
Difference in percentages of participants with seroresponse at 1 month after vaccination course							
SARS-CoV-2 neutralisation assay - NT50 (titre)[e]							
Age	**N[a]**	**n[f] (%) (95% CI[g]) (1 month after Dose 3)**	**Age**	**N[a]**	**n[f] (%) (95% CI[g]) (1 month after Dose 2)**	**Age**	**Difference in seroresponse rates %[h] (95% CI[i])[j]**
2 to 4 years	141	141(100.0) (97.4, 100.0)	16 to 25 years of age	170	168 (98.8) (95.8, 99.9)	2 to 4 years/16 to 25 years of age	1.2 (1.5, 4.2)
6 to 23 months	80	80 (100.0) (95.5, 100.0)	16 to 25 years of age	170	168 (98.8) (95.8, 99.9)	6 to 23 months years/16 to 25 years of age	1.2 (3.4, 4.2)

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

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

Note: Seroresponse is defined as achieving a ≥ 4-fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a post-vaccination 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 dose/sampling time point for GMTs and number of participants with valid and determinate assay results for the specified assay at both baseline and the given dose/sampling time point for seroresponse rates.
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 mean difference of the logarithms of the titres (younger age group minus 16 to 25 years of age) and the corresponding CI (based on the Student t distribution).
d. For each younger age group (2 to 4 years, 6 to 23 months), immunobridging based on GMR is declared if the lower bound of the 2-sided 95% CI for the GMR ratio is greater than 0.67 and the point estimate of the GMR is ≥ 0.8.
e. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralisation Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus 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.
f. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.
g. Exact 2-sided CI based on the Clopper and Pearson method.
h. Difference in proportions, expressed as a percentage (younger age group minus 16 to 25 years of age).
i. 2-sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
j. For each younger age group (2 to 4 years, 6 to 23 months), immunobridging based on seroresponse rate is declared if the lower bound of the 2-sided 95% CI for the difference in proportions is greater than -10.0% provided that the immunobridging criteria based on GMR were met.

Immunogenicity in immunocompromised participants (adults and children)
Study 10 is a Phase 2b, open-label study (n = 124) that enrolled immunocompromised participants 2 to < 18 years of age receiving immunomodulator therapy or who have undergone solid organ transplant (within the previous 3 months) and are on immunosuppression or who have undergone bone marrow or stem cell transplant at least 6 months prior to enrolment and in immunocompromised participants 18 years of age and older treated for non-small cell lung cancer (NSCLC) or chronic lymphocytic leukaemia (CLL), receiving haemodialysis for secondary to end-stage renal disease, or receiving immunomodulator therapy for an autoimmune inflammatory disorder. Participants received 4 age-appropriate doses of Comirnaty (3 mcg, 10 mcg, or 30 mcg); the first 2 doses separated by 21 days, with the third dose occurring 28 days after the second dose, followed by a fourth dose, 3 to 6 months after Dose 3.

Analysis of immunogenicity data at 1 month after Dose 3 (26 participants 2 to < 5 years of age, 56 participants 5 to < 12 years of age, 11 participants 12 to < 18 years of age, and 4 participants ≥ 18 years of age) and 1 month after Dose 4 (16 participants 2 to < 5 years of age, 31 participants 5 to < 12 years of age, 6 participants 12 to < 18 years of age, and 4 participants ≥ 18 years of age) in the evaluable immunogenicity population without evidence of prior infection demonstrated a vaccine-elicited immune response. GMTs were observed to be substantially higher at 1 month after Dose 3 and further increased at 1 month after Dose 4 and remained high at 6 months after Dose 4 compared to levels observed before study vaccination across age groups and disease subsets.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Comirnaty in one or more subsets of the paediatric population in prevention of COVID-19 (see section 4.2 for information on paediatric use).

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 post-natal day 21 as well as in foetuses and offspring. There were no vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development. No Comirnaty data are available on vaccine placental transfer or excretion in milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

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

6.3 Shelf life

The storage and handling conditions printed on the vial or carton labels may differ from those in this product information. In these circumstances, the conditions in the product information should be followed.

Unopened vials

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.

18 months when stored at -90 °C to -60 °C.
Within the 18-month shelf life the thawed (previously frozen) vials may be stored at 2 °C to 8 °C for up to 10 weeks.

Thawing procedure
When stored frozen at -90 °C to -60 °C, 10-vial packs of the vaccine can be thawed at 2 °C to 8 °C for:

- **Orange cap:** 4 hours
- **Maroon or yellow cap:** 2 hours

Thawed (previously frozen) vials
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.

Thawed vials can be handled in room light conditions.

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

Opened vial

Once the vaccine vial is diluted, it should be used immediately or within 6 hours and kept at 2 °C to 8 °C.

6.4 Special precautions for storage

Store in a freezer at -90 °C to -60 °C.
Store in the original package in order to protect from light.
During storage, minimise exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.

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

6.5 Nature and contents of container

Orange cap (10-dose vial)

1.3 mL concentrate for dispersion in a 2 mL clear multidose vial (type I glass) with a stopper (synthetic bromobutyl rubber) and an **orange flip-off plastic cap** with aluminium seal. Each vial contains **10 doses**, see section 6.6.

Pack size: 10 vials

Maroon cap (10-dose vial)

0.4 mL concentrate for dispersion in a 2 mL clear multidose vial (type I glass) with a stopper (synthetic bromobutyl rubber) and a **maroon flip-off plastic cap** with aluminium seal. Each vial contains **10 doses**, see section 6.6.

Pack size: 10 vials

Yellow cap (3-dose vial)

0.48 mL concentrate for dispersion in a 2 mL clear multidose vial (type I glass) with a stopper (synthetic bromobutyl rubber) and a **yellow flip-off plastic cap** with aluminium seal. Each vial contains **3 doses**, see section 6.6.

Pack size: 10 vials

6.6 Special precautions for disposal and other handling

The storage and handling conditions printed on the vial or carton labels may differ from those in this product information. In these circumstances, the conditions in the product information should be followed.

Orange cap (10-dose vial) or maroon cap (10-dose vial)

*Handling instructions prior to use for a vial with an **orange cap** or **maroon cap***
Comirnaty JN.1 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- **Verify** that the vial has either:
  - **an orange plastic cap** and the product **name is Comirnaty JN.1 10 micrograms/dose concentrate for dispersion for injection** (children 5 to 11 years), or
  - a **maroon plastic cap** and the product **name is Comirnaty JN.1 3 micrograms/dose concentrate for dispersion for injection** (infants and children 6 months to 4 years).
- If the vial has another product name on the label or a different cap colour, please make reference to the WHO Product Information for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 10-vial pack may take:
  - **Orange cap:** 4 hours to thaw
  - **Maroon cap:** 2 hours to thaw
- Ensure vials are completely thawed prior to use.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Thawed vials can be handled in room light conditions.

*Dilution for a vial with an **orange cap** or **maroon cap***

- Allow the thawed vial to come to room temperature and gently invert it 10 times prior to dilution. Do not shake.
- Prior to dilution, the thawed dispersion may contain white to off-white opaque amorphous particles.
- The thawed vaccine must be diluted in its original vial with:
  - **Orange cap: 1.3 mL sodium chloride 9 mg/mL (0.9%) solution for injection**, using a 21 gauge or narrower needle and aseptic techniques.
  - **Maroon cap: 2.2 mL sodium chloride 9 mg/mL (0.9%) solution for injection**, using a 21 gauge or narrower needle and aseptic techniques.
- Equalise vial pressure before removing the needle from the vial stopper by withdrawing air into the empty diluent syringe.
- Gently invert the diluted dispersion 10 times. Do not shake.
- The diluted vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discolouration are present.
- The diluted vials should be marked with the appropriate **discard date and time**.
- **After dilution**, store at 2 ºC to 8 ºC and use within **6 hours**.
- Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.

*Preparation of **0.2 mL** doses using a vial with an **orange cap** or **maroon cap***

- After dilution, the vial contains 2.6 mL from which 10 doses of 0.2 mL can be extracted.
- Using aseptic technique, cleanse the vial stopper with a single use antiseptic swab.
- Withdraw 0.2 mL of Comirnaty JN.1.
- **Low dead-volume syringes and/or needles** should be used in order to extract 10 doses from a single vial. The low dead-volume syringe and needle combination should have a dead-volume

of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract ten doses from a single vial.
- Each dose must contain **0.2 mL** of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of **0.2 mL**, discard the vial and any excess volume.
- Discard any unused vaccine within 6 hours after dilution.

Yellow cap (3-dose vial)

*Handling instructions prior to use for a vial with a **yellow cap***
Comirnaty JN.1 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.
- **Verify** that the vial has a **yellow plastic cap** and the product **name is Comirnaty JN.1 3 micrograms/dose concentrate for dispersion for injection** (infants and children 6 months to 4 years).
- If the vial has another product name on the label, or a different cap colour, please make reference to the WHO Product Information for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 10-vial pack may take 2 hours to thaw. Ensure vials are completely thawed prior to use.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Thawed vials can be handled in room light conditions.

*Dilution for a vial with a **yellow cap***
- Allow the thawed vial to come to room temperature and gently invert it 10 times prior to dilution. Do not shake.
- Prior to dilution, the thawed dispersion may contain white to off-white opaque amorphous particles.
- The thawed vaccine must be diluted in its original vial with **1.1 mL sodium chloride 9 mg/mL (0.9%) solution for injection**, using a 21 gauge or narrower needle and aseptic techniques.
- Equalise vial pressure before removing the needle from the vial stopper by withdrawing 1.1 mL air into the empty diluent syringe.
- Gently invert the diluted dispersion 10 times. Do not shake.
- The diluted vaccine should present as a clear to slightly opalescent dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discolouration are present.
- The diluted vials should be marked with the appropriate **discard date and time**.
- **After dilution**, store at 2 ºC to 8 ºC and use within **6 hours**.
- Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.

*Preparation of **0.3 mL** doses using a vial with a **yellow cap***
- After dilution, the vial contains 1.58 mL from which **3 doses** of **0.3 mL** can be extracted.
- Using aseptic technique, cleanse the vial stopper with a single use antiseptic swab.
- Withdraw **0.3 mL** of Comirnaty JN.1 for infants and children aged 6 months to 4 years. **Standard syringes and/or needles** can be used in order to extract 3 doses from a single vial.
- Each dose must contain **0.3 mL** of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of **0.3 mL**, discard the vial and any excess volume.
- Discard any unused vaccine within 6 hours after dilution.

Disposal

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

7. MANUFACTURER

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▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Comirnaty LP.8.1 30 micrograms/dose dispersion for injection
Comirnaty LP.8.1 10 micrograms/dose dispersion for injection
COVID-19 mRNA Vaccine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Do not dilute prior to use.

Table 1. Comirnaty LP.8.1 qualitative and quantitative composition

Product presentation	**Container**	**Dose(s) per container (see sections 4.2 and 6.6)**	**Contents per dose**
Comirnaty LP.8.1 30 micrograms/dose dispersion for injection	Multidose (2.25 mL) vial (grey cap)	6 doses of 0.3 mL	One dose (0.3 mL) contains 30 micrograms of mRNA encoding LP.8.1, a COVID−19 mRNA Vaccine (nucleoside modified, embedded in lipid nanoparticles).
Comirnaty LP.8.1 10 micrograms/dose dispersion for injection	Single dose vial (blue cap)	1 dose of 0.3 mL	One dose (0.3 mL) contains 10 micrograms of mRNA encoding LP.8.1, a COVID−19 mRNA Vaccine (nucleoside modified, embedded in lipid nanoparticles).
	Multidose (2.25 mL) vial (blue cap)	6 doses of 0.3 mL	

The mRNA encoding LP.8.1 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 LP.8.1).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersion for injection.

Comirnaty LP.8.1 30 micrograms/dose dispersion for injection is a white to off-white dispersion (pH: 6.9 - 7.9).

Comirnaty LP.8.1 10 micrograms/dose dispersion for injection is a clear to slightly opalescent dispersion (pH: 6.9 - 7.9).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Comirnaty LP.8.1 dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 5 years of age and older.

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

4.2 Posology and method of administration

Posology

Individuals 12 years of age and older
Comirnaty LP.8.1 30 micrograms/dose dispersion for injection 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 LP.8.1 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Children 5 to 11 years of age (i.e. 5 to less than 12 years of age)
Comirnaty LP.8.1 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 and 5.1).

For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty LP.8.1 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Severely immunocompromised individuals
Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations (see section 4.4).

Paediatric population
There are paediatric formulations available for infants and children aged 6 months to 4 years. For details, please refer to the WHO Product Information for other formulations.

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

Elderly population
No dose adjustment is required in elderly individuals 65 years of age and older.

Method of administration

Comirnaty LP.8.1 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.

Single dose vials
Single dose vials of Comirnaty LP.8.1 contain 1 dose of 0.3 mL of vaccine.
- Withdraw a single 0.3 mL dose of Comirnaty LP.8.1.
- Discard vial and any excess volume.
- Do not pool excess vaccine from multiple vials.

Multidose vials
Multidose vials of Comirnaty LP.8.1 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
Safety and immunogenicity have been assessed in a limited number of immunocompromised individuals, including those receiving immunosuppressant therapy (see sections 4.8 and 5.1). The efficacy of Comirnaty LP.8.1 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 LP.8.1 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

Comirnaty LP.8.1 30 micrograms/dose dispersion for injection may be administered concomitantly with seasonal influenza vaccine.

In individuals 18 years of age and older, Comirnaty LP.8.1 may be administered concomitantly with a pneumococcal conjugate vaccine (PCV).

In individuals 18 years of age and older, Comirnaty LP.8.1 may be administered concomitantly with an unadjuvanted recombinant protein respiratory syncytial virus (RSV) vaccine.

In individuals 65 years of age and older, Comirnaty LP.8.1 may be administered concomitantly with an unadjuvanted recombinant protein RSV vaccine and a high dose influenza vaccine.

Different injectable vaccines should be administered at different injection sites.

Concomitant administration of Comirnaty LP.8.1 10 micrograms/dose dispersion for injection with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

No data are available yet regarding the use of Comirnaty LP.8.1 during pregnancy.

However, there are limited clinical study data (less than 300 pregnancy outcomes) from the use of Comirnaty in pregnant participants. 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 LP.8.1 can be used during pregnancy.

Breast-feeding

No data are available yet regarding the use of Comirnaty LP.8.1 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 LP.8.1 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).

4.7 Effects on ability to drive and use machines

Comirnaty LP.8.1 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 LP.8.1 is inferred from safety data of the prior Comirnaty vaccines.

Initially approved Comirnaty vaccine
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 3 109 children 5 to 11 years of age received at least 1 dose of the initially approved Comirnaty vaccine 10 mcg and a total of 1 538 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, 2 206 (1 481 Comirnaty 10 mcg and 725 placebo) children have been followed for ≥ 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 (≥ 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 2 408 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, 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.

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 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.

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 ≥ 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.

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.

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.

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 6.3 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 myalgia (> 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%), myalgia (> 20%), chills (> 10%), and arthralgia (> 10%).

Participants 12 years of age and older – after a booster dose of Comirnaty Omicron XBB.1.5 (fourth dose or more)
In a subset from Study 13 (Phase 2/3), 412 participants 12 years of age and older, who had received at least 3 doses of an authorised mRNA COVID-19 vaccine, received a booster (fourth dose or more) of Comirnaty Omicron XBB.1.5 2.0 to 24.1 months after receiving Dose 3. Participants who received a booster (fourth dose or more) of Comirnaty XBB.1.5 had a median follow-up time of 6.3 months.

The safety profile of Comirnaty Omicron XBB.1.5 was similar to the overall Comirnaty safety profile.

Participants 12 years of age and older – after a single dose of Comirnaty Omicron XBB.1.5
In a subset from Study 13 (Phase 2/3), 311 participants 12 years of age and older who were considered to be baseline SARS-CoV-2 positive and COVID-19 vaccine-naïve, received 1 dose of Comirnaty Omicron XBB.1.5. Participants had a median follow-up time of 6.4 months.

The safety profile of Comirnaty Omicron XBB.1.5 was similar to the overall Comirnaty safety profile. The most frequent adverse reactions in participants were injection site pain (> 50%), fatigue (> 30%), headache (> 20%), myalgia, diarrhoea, arthralgia, chills and injection site swelling (> 10%).

Participants 12 years of age and older – after a single dose of Comirnaty Omicron JN.1
In a subset from Study 13 (Phase 2/3), 216 participants 12 years of age and older received 1 dose of Comirnaty Omicron JN.1 and had a median follow-up time of 6.3 months.

The safety profile of Comirnaty Omicron JN.1 was similar to the overall Comirnaty safety profile. The most frequent adverse reactions in participants were injection site pain (> 60%), fatigue (> 30%), headache (>20%), myalgia, chills and injection site swelling (> 10%).

Participants 18 years of age and older – after a single dose of Comirnaty Omicron KP.2
In a subset from Study 13 (Phase 2/3), 102 participants 18 years of age and older received 1 dose of Comirnaty Omicron KP.2 and had a median follow-up time of 6.3 months.

The safety profile of Comirnaty Omicron KP.2 was similar to the overall Comirnaty safety profile. The most frequent adverse reactions in participants were injection site pain (> 50%), fatigue (> 40%), headache and myalgia (> 20%).

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 and post-authorisation experience 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 2. 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

System Organ Class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Common	Lymphadenopathy[a]
Immune system disorders	Uncommon	Hypersensitivity reactions (e.g. rash, pruritus, urticaria[b], angioedema[b])
	Not known	Anaphylaxis
Metabolism and nutrition disorders	Uncommon	Decreased appetite
Psychiatric disorders	Uncommon	Insomnia

System Organ Class	Frequency	Adverse reactions
Nervous system disorders	Very common	Headache
	Uncommon	Dizziness[d]; lethargy
	Rare	Acute peripheral facial paralysis[c]
	Not known	Paraesthesia[d]; hypoaesthesia[d]
Cardiac disorders	Very rare	Myocarditis[d]; pericarditis[d]
Gastrointestinal disorders	Very common	Diarrhoea[d]
	Common	Nausea; vomiting[d,j]
Skin and subcutaneous tissue disorder	Uncommon	Hyperhidrosis; night sweats
	Not known	Erythema multiforme[d]
Musculoskeletal and connective tissue disorders	Very common	Arthralgia; myalgia
	Uncommon	Pain in extremity[e]
Reproductive system and breast disorders	Not known	Heavy menstrual bleeding[i]
General disorders and administration site conditions	Very common	Injection site pain; fatigue; chills; pyrexia[f]; injection site swelling
	Common	Injection site redness[h]
	Uncommon	Asthenia; malaise; injection site pruritus
	Not known	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. Injection site redness occurred at a higher frequency (very common) in children 5 to 11 years of age and in immunocompromised participants 5 years of age and older.
i. Most cases appeared to be non-serious and temporary in nature.
j. The frequency category for vomiting was very common in pregnant women 18 years of age and older and in immunocompromised participants 5 to 18 years of age.

Special populations

Infants born to pregnant participants – after 2 doses of Comirnaty
Study C4591015 (Study 9), a Phase 2/3, placebo-controlled study, evaluated a total of 346 pregnant participants who received Comirnaty (n = 173) or placebo (n = 173). Infants (Comirnaty n = 167 or placebo n = 168) were evaluated up to 6 months. No safety concerns were identified that were attributable to maternal vaccination with Comirnaty.

Immunocompromised participants (adults and children)
In study C4591024 (Study 10), a total of 124 immunocompromised participants 2 years of age and older received Comirnaty (see section 5.1).

Safety with concomitant vaccine administration

Concomitant administration with seasonal influenza vaccine
In Study 8, a Phase 3 study, participants 18 to 64 years of age who received Comirnaty coadministered with seasonal inactivated influenza vaccine (SIIV), quadrivalent followed 1 month later by placebo, were compared to participants who received an inactivated influenza vaccine with placebo followed 1 month later by Comirnaty alone (n = 553 to 564 participants in each group).

Concomitant administration with pneumococcal conjugate vaccine
In Study 11 (B7471026), a Phase 3 study, participants 65 years of age and older who received a booster dose of Comirnaty coadministered with 20-valent pneumococcal conjugate vaccine (20vPNC) (n = 187) were compared to participants who received Comirnaty alone (n = 185).

Concomitant administration with an unadjuvanted recombinant protein RSV vaccine or with an unadjuvanted recombinant protein RSV vaccine and a high dose influenza vaccine
In Study 12 (C5481001), a Phase 1/2 study, participants 65 years of age and older who received Comirnaty Original/Omicron BA.4-5 and RSV vaccine coadministered in one arm plus high dose quadrivalent influenza vaccine (QIV) (n = 158) or placebo (n = 157) in the opposite arm were compared to participants who received the individual vaccines given with placebo.

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 via the national reporting system.

4.9 Overdose

There have been reports of higher than recommended doses of Comirnaty in clinical trials and post-authorisation experience. In general, adverse events reported with overdoses have been similar to the known adverse reaction profile of Comirnaty.

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) with Comirnaty and Comirnaty Original/Omicron BA.4-5
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 3.

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

		Vaccine group (as assigned/randomised)				
		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
SARS-CoV-2 neutralisation assay	Sampling time point[a]	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])	GMR[d] (95% CI[d])
Omicron BA.4-5 - NT50 (titre)[e]	Pre-vaccination	102	488.3 (361.9, 658.8)	112	248.3 (187.2, 329.5)	-
	1 month	102	2 189.9 (1 742.8, 2 751.7)	113	1 393.6 (1 175.8, 1 651.7)	1.12 (0.92, 1.37)
Reference strain - NT50 (titre)[e]	Pre-vaccination	102	2 904.0 (2 372.6, 3 554.5)	113	1 323.1 (1 055.7, 1 658.2)	-
	1 month	102	8 245.9 (7 108.9, 9 564.9)	113	7 235.1 (6 331.5, 8 267.8)	-

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 × 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 vaccine-naïve participants 12 years of age and older – after a single dose of Comirnaty Omicron XBB.1.5

In an analysis of a subset from Study 13, 302 vaccine-naïve participants 12 years of age and older who were considered to be SARS-CoV-2 positive at baseline and who received 1 dose of Comirnaty Omicron XBB.1.5 were compared to participants who received Comirnaty Omicron XBB.1.5 after at least 3 doses of an mRNA COVID-19 vaccine. The evaluable immunogenicity population who were vaccine-naïve had a median age of 36.0 years and comprised of 62.6% White and 50.7% Hispanic/Latino participants. The evaluable immunogenicity population who were vaccine experienced (n=296) had a median age of 55 years and comprised of 79.4% White and 18.6% Hispanic/Latino.

Neutralising titres against Omicron XBB.1.5 increased from baseline to 1 month after study vaccination and were greater in participants receiving Comirnaty Omicron XBB.1.5 as a single dose compared with participants who received Comirnaty Omicron XBB.1.5 after at least 3 doses of an mRNA COVID-19 vaccine. Noninferiority was met with respect to the geometric mean ratio (GMR) of Omicron XBB.1.5-neutralising titres, and the difference in seroresponse to the XBB.1.5 strain in vaccine-naïve participants compared to participants who received Comirnaty Omicron XBB.1.5 after at least 3 doses of an mRNA COVID-19 vaccine (Table 4).

Table 4. Geometric mean ratio and difference in percentages of participants with seroresponse – Study 13 vaccine-naïve and subset of vaccine-experienced – evaluable immunogenicity population

		Vaccine group (as assigned)				Group comparison	
		Vaccine-naïve Comirnaty Omicron XBB.1.5 30 mcg		Vaccine-experienced Comirnaty Omicron XBB.1.5 30 mcg		Vaccine-naïve Comirnaty Omicron XBB.1.5 30 mcg / Vaccine-experienced Comirnaty Omicron XBB.1.5 30 mcg	
SARS-CoV-2 neutralisation assay Omicron XBB.1.5 - NT50 (titre)[e]	**Sampling time point[a]**	**n[b]**	**GMT[c] (95% CI[c])**	**n[b]**	**GMT[c] (95% CI[c])**	**GMR[d] (95% CI[d])**	
Geometric mean 50% neutralising titre (GMT)	1 month	299	4 373.4 (3 757.1, 5 090.9)	296	2 915.7 (2 462.4, 3 452.5)	1.93 (1.52, 2.44)[f]	
	Sampling time point[a]	**N[g]**	**n[h] (%) (95% CI[i])**	**N[g]**	**n[h] (%) (95% CI[i])**	**Difference %[j]**	**(95% CI[k])**
Seroresponse rate (%) for 50% neutralising titre	1 month	298	253 (84.9) (80.3, 88.8)	295	218 (73.9) (68.5, 78.8)	7.31	(1.34, 13.28)[l]

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 both the pre−vaccination time point and 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. GMRs and the corresponding 2-sided 95% CIs were calculated by exponentiating the difference in least square means and the corresponding CIs based on a linear regression model with baseline assay results (log scale), age, and vaccine group as covariates.
e. SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (Omicron subvariant XBB.1.5).
f. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67.

g. 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. These values are the denominators for the percentage calculations.
h. n = Number of participants with a seroresponse for the given assay at the given sampling time point.
i. Exact 2-sided CI, based on the Clopper and Pearson method.
j. Difference in proportions, expressed as a percentage.
k. 2-Sided CI, based on the Miettinen and Nurminen method stratified by baseline neutralising titre category (< median, ≥ median) and age group (< median, ≥ median). The median of baseline neutralising titres and median age was calculated based on the pooled data in 2 comparator groups.
l. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is > -10%.

Immunogenicity in participants 12 years of age and older – after a single dose of Comirnaty Omicron JN.1

In an analysis of a subset from Study 13, 212 participants 12 years of age and older who received 1 dose of Comirnaty Omicron JN.1 were compared to 200 participants who received Comirnaty Omicron XBB.1.5 after receiving at least 3 doses of an mRNA COVID-19 vaccine. The evaluable immunogenicity population who received Comirnaty Omicron JN.1 had a median age of 54.5 years and comprised of 69.3% White and 23.1% Hispanic/Latino participants, and 87.3% were positive for SARS-CoV-2 at baseline, and 89.2% had previously received a COVID-19 vaccine.

Neutralising titres and seroresponse against Omicron JN.1 or Omicron XBB.5 in participants receiving Comirnaty Omicron JN.1 or Comirnaty Omicron XBB.1.5 are presented in Table 5.

Table 5. Geometric mean titres and percentage of participants achieving seroresponse – Comirnaty JN.1 or Comirnaty XBB.1.5 – participants 12 years of age and older – evaluable immunogenicity population

		Comirnaty Omicron JN.1 30 mcg		Comirnaty Omicron XBB.1.5 30 mcg	
Geometric mean 50% neutralising titre (GMT)	**Sampling time point[a]**	**n[b]**	**GMT[c] (95% CI[c])**	**n[b]**	**GMT[c] (95% CI[c])**
SARS-CoV-2 neutralisation assay – Omicron JN.1 - NT50 (titre)[d]	Pre-vaccination	211	190.4 (153.6, 235.9)	198	155.5 (126.6, 190.8)
	1 month	212	2203.3 (1855.7, 2616.0)	199	1133.8 (950.7, 1352.2)
SARS-CoV-2 neutralisation assay – Omicron XBB.1.5 – NT50 (titre)[e]	Pre-vaccination	212	290.3 (233.0, 361.6)	200	219.2 (177.5, 270.7)
	1 month	212	2364.4 (1917.4, 2915.6)	200	2848.1 (2341.9, 3463.8)
Seroresponse rate for 50% neutralising titre	**Sampling time point[a]**	**N[f]**	**n[g] (%) (95% CI[h])**	**N[b]**	**n[g] (%) (95% CI[h])**
SARS-CoV-2 neutralisation assay – Omicron JN.1 - NT50 (titre)[d]	1 month	211	149 (70.6) (64.0, 76.7)	197	129 (65.5) (58.4, 72.1)
SARS-CoV-2 neutralisation assay – Omicron XBB.1.5 – NT50 (titre)[e]	1 month	212	128 (60.4) (53.5, 67.0)	200	164 (82.0) (76.0, 87.1)

Abbreviations: 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 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 (Omicron subvariant JN.1).
e. SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (Omicron subvariant XBB.1.5).
f. 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. These values are the denominators for the percentage calculations.
g. n = Number of participants with a seroresponse for the given assay at the given sampling time point.
h. Exact 2-sided CI, based on the Clopper and Pearson method.

Immunogenicity in participants 12 years of age and older – after a single dose of Comirnaty Omicron KP.2

In an analysis of a subset from Study 13, 100 participants 18 years of age and older who received 1 dose of Comirnaty Omicron KP.2 were compared to 194 participants who received 1 dose of

Comirnaty Omicron JN.1. The evaluable immunogenicity population who received Comirnaty Omicron KP.2 had a median age of 55.0 years and comprised of 75.0% White and 15.0% Hispanic/Latino participants, 91.0% were positive for SARS-CoV-2 at baseline, and 90.0% had previously received a COVID-19 vaccine.

Neutralising titres and seroresponse against Omicron KP.2 and Omicron JN.1 in participants receiving Comirnaty Omicron KP.2 or Comirnaty Omicron JN.1 are presented in Table 6.

Table 6. Geometric mean titres and percentage of participants achieving seroresponse – Comirnaty KP.2 or Comirnaty JN.1 – participants 18 years of age and older – evaluable immunogenicity population

		Comirnaty Omicron KP.2 30 mcg		Comirnaty Omicron JN.1 30 mcg	
Geometric mean 50% neutralising titre (GMT)	**Sampling time point[a]**	**n[b]**	**GMT[c] (95% CI[c])**	**n[b]**	**GMT[c] (95% CI[c])**
SARS-CoV-2 neutralisation assay – Omicron KP.2 – NT50 (titre)[d]	Pre-vaccination	99	207.6 (150.0, 287.4)	194	78.3 (64.2, 95.6)
	1 month	100	2256.5 (1660.2, 3067.0)	194	873.3 (706.1, 1080.2)
SARS-CoV-2 neutralisation assay – Omicron JN.1 – NT50 (titre)[e]	Pre-vaccination	100	492.5 (359.8, 674.0)	194	185.1 (148.1, 231.4)
	1 month	100	4319.5 (3280.7, 5687.2)	194	2088.6 (1743.9, 2501.5)
Seroresponse rate for 50% neutralising titre	**Sampling time point[a]**	**N[f]**	**n[g] (%) (95% CI[h])**	**N[b]**	**n[g] (%) (95% CI[h])**
SARS-CoV-2 neutralisation assay – Omicron KP.2 – NT50 (titre)[d]	1 month	99	76 (76.8) (67.2, 84.7)	194	130 (67.0) (59.9, 73.6)
SARS-CoV-2 neutralisation assay – Omicron JN.1 – NT50 (titre)[e]	1 month	100	64 (64.0) (53.8, 73.4)	194	137 (70.6) (63.7, 76.9)

Abbreviations: 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 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 (Omicron subvariant KP.2).
e. SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (Omicron subvariant JN.1).
f. 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. These values are the denominators for the percentage calculations.
g. n = Number of participants with a seroresponse for the given assay at the given sampling time point.
h. Exact 2-sided CI, based on the Clopper and Pearson method.

Initially approved Comirnaty vaccine

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 hospitalisation 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/m^2, chronic pulmonary disease, diabetes mellitus, hypertension).

The vaccine efficacy information is presented in Table 7.

Table 7. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of 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 2.214 (17 411)	162 2.222 (17 511)	95.0 (90.0, 97.9)
16 to 64 years	7 1.706 (13 549)	143 1.710 (13 618)	95.1 (89.6, 98.1)
65 years and older	1 0.508 (3 848)	19 0.511 (3 880)	94.7 (66.7, 99.9)
65 to 74 years	1 0.406 (3 074)	14 0.406 (3 095)	92.9 (53.1, 99.8)
75 years and older	0 0.102 (774)	5 0.106 (785)	100.0 (-13.1, 100.0)

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

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

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 8.

Table 8. 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 6.247 (20 712)	850 6.003 (20 713)	91.3 (89.0, 93.2)
16 to 64 years	70 4.859 (15 519)	710 4.654 (15 515)	90.6 (87.9, 92.7)
65 years and older	7 1.233 (4 192)	124 1.202 (4 226)	94.5 (88.3, 97.8)
65 to 74 years	6 0.994 (3 350)	98 0.966 (3 379)	94.1 (86.6, 97.9)
75 years and older	1 0.239 (842)	26 0.237 (847)	96.2 (76.9, 99.9)

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

* Participants who had no evidence of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
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 9) 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 9. 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 8.439[e] (22 505)	30 8.288[e] (22 435)	96.7 (80.3, 99.9)
7 days after Dose 2[f]	1 6.522[g] (21 649)	21 6.404[g] (21 730)	95.3 (70.9, 99.9)

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, non−invasive 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.

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 10. 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 10. 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

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*			
	COVID-19 mRNA Vaccine 10 mcg/dose N[a]=1 305 Cases n1[b] Surveillance time[c] (n2[d])	**Placebo N[a]=663 Cases n1[b] Surveillance time[c] (n2[d])**	**Vaccine efficacy % (95% CI)**
Children 5 to 11 years of age	3 0.322 (1 273)	16 0.159 (637)	90.7 (67.7, 98.3)

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

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

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

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

c. Total surveillance time in 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.

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 2 703 participants who received the vaccine and 42 cases out of 1 348 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 3 018 who received vaccine and 42 cases in 1 511 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 pre-specified 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 11.

Table 11. 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			
		10 mcg/dose 5 to 11 years N[a]=264	30 mcg/dose 16 to 25 years N[a]=253	5 to 11 years/ 16 to 25 years	
	Time point[b]	GMT[c] (95% CI[c])	GMT[c] (95% CI[c])	GMR[d] (95% CI[d])	Met immunobridging objective[e] (Y/N)
Geometric mean 50% neutralising titre[f] (GMT[c])	1 month after Dose 2	1 197.6 (1 106.1, 1 296.6)	1 146.5 (1 045.5, 1 257.2)	1.04 (0.93, 1.18)	Y
	Time point[b]	**n[g] (%) (95% CI[h])**	**n[g] (%) (95% CI[h])**	**Difference %[i] (95% CI[j])**	**Met immunobridging objective[k] (Y/N)**
Seroresponse rate (%) for 50% neutralising titre[f]	1 month after Dose 2	262 (99.2) (97.3, 99.9)	251 (99.2) (97.2, 99.9)	0.0 (-2.0, 2.2)	Y

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

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

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

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 12. 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 12. 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 0.823 (4 659)	123 0.792 (4 614)	95.3 (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 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 to 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 summarised in Table 13.

Table 13. Summary of geometric mean titres – NT50 – participants without evidence of infection – phase 2/3 – immunogenicity set – 5 to 11 years of age – evaluable immunogenicity population

	Sampling time point[a]		
Assay	1 month after booster dose (n[b]=67) GMT[c] (95% CI[c])	1 month after dose 2 (n[b]=96) GMT[c] (95% CI[c])	1 month after booster dose/ 1 month after dose 2 GMR[d] (95% CI[d])
SARS-CoV-2 neutralisation assay - NT50 (titre)	2 720.9 (2 280.1, 3 247.0)	1 253.9 (1 116.0, 1 408.9)	2.17 (1.76, 2.68)

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

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 × 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).

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 pregnant participants and infants born to pregnant participants – after 2 doses with Comirnaty

Study 9 was a Phase 2/3 multinational, placebo-controlled, observer-blind study that enrolled pregnant participants 18 years of age and older to receive 2 doses of Comirnaty (n = 173) or placebo (n = 173). Pregnant participants received Dose 1 of Comirnaty at 24 to 34 weeks gestation and the majority (90.2%) received the second dose 19 to 23 days after Dose 1.

Descriptive immunogenicity analysis was performed in pregnant participants receiving Comirnaty in Study 9 compared to a comparator subset of nonpregnant participants from Study 2 evaluating the ratio of the neutralising GMT (GMR) 1 month after Dose 2. The evaluable immunogenicity population who received Comirnaty in the pregnant participants group in Study 9 (n = 111) and in nonpregnant

participants in Study 2 (n = 114) had a median age of 30 years (range 18 to 44 years of age) and comprised of 37.8% vs 3.5% with a positive baseline SARS-CoV-2 status, respectively.

Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, the observed SARS-CoV-2 50% neutralising GMT 1 month after Dose 2 was lower in the pregnant participants (Study 9) when compared to nonpregnant female participants (Study 2) (the ratio of the GMT [GMR] was 0.67 (95% CI: 0.50, 0.90).

Among participants with or without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, the model-adjusted GMT 1 month after Dose 2 was similar in the pregnant participants when compared to nonpregnant female participants (the model-adjusted ratio of the GMT [GMR] was 0.95 (95% CI: 0.69, 1.30)). The model-adjusted GMT and GMR were calculated based on a regression model adjusting for age and baseline neutralising titres.

Immunogenicity in immunocompromised participants (adults and children)
Study 10 is a Phase 2b, open-label study (n = 124) that enrolled immunocompromised participants 2 to < 18 years of age receiving immunomodulator therapy or who have undergone solid organ transplant (within the previous 3 months) and are on immunosuppression or who have undergone bone marrow or stem cell transplant at least 6 months prior to enrolment and in immunocompromised participants 18 years of age and older treated for non-small cell lung cancer (NSCLC) or chronic lymphocytic leukaemia (CLL), receiving haemodialysis for secondary to end-stage renal disease, or receiving immunomodulator therapy for an autoimmune inflammatory disorder. Participants received 4 age-appropriate doses of Comirnaty (3 mcg, 10 mcg, or 30 mcg); the first 2 doses separated by 21 days, with the third dose occurring 28 days after the second dose, followed by a fourth dose, 3 to 6 months after Dose 3.

Analysis of immunogenicity data at 1 month after Dose 3 (26 participants 2 to < 5 years of age, 56 participants 5 to < 12 years of age, 11 participants 12 to < 18 years of age, and 4 participants ≥ 18 years of age) and 1 month after Dose 4 (16 participants 2 to < 5 years of age, 31 participants 5 to < 12 years of age, 6 participants 12 to < 18 years of age, and 4 participants ≥ 18 years of age) in the evaluable immunogenicity population without evidence of prior infection demonstrated a vaccine-elicited immune response. GMTs were observed to be substantially higher at 1 month after Dose 3 and further increased at 1 month after Dose 4 and remained high at 6 months after Dose 4 compared to levels observed before study vaccination across age groups and disease subsets.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Comirnaty in one or more subsets of the paediatric population in prevention of COVID-19 (see section 4.2 for information on paediatric use).

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 post-natal 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

The storage and handling conditions printed on the vial or carton labels may differ from those in this product information. In these circumstances, the conditions in the product information should be followed.

Confirm the storage conditions listed for the frozen and refrigerated only vials.

Frozen vials have printed EXP at -90 °C to -60 °C.
Refrigerated only vials have printed EXP at 2 °C to 8 °C.

Unopened frozen vials

Single dose and multidose vials
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.

18 months when stored at -90 °C to -60 °C.
Within the 18-month shelf life the thawed (previously frozen) vials may be stored at 2 °C to 8 °C for up to 10 weeks.

Thawing procedure
Single dose vials
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.

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.

Thawed (previously frozen) vials
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.

Thawed vials can be handled in room light conditions.

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

Unopened refrigerated only vials

Multidose vials
The vaccine will be received and stored at 2 °C to 8 °C (refrigerated only).
12 months when stored at 2 °C to 8 °C.

Opened vials

Once the vaccine vial is punctured it should be used immediately or within 6 hours and kept at 2 °C to 8 °C.

6.4 Special precautions for storage

Frozen vials

Store single dose frozen vials and multidose frozen vials in a freezer at -90 °C to -60 °C.

Refrigerated only vials

Store refrigerated only vials at 2 °C to 8 °C. DO NOT FREEZE.

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

Table 14. Comirnaty LP.8.1 nature and contents of container

Product presentation	**Contents**	**Container**	**Dose(s) per container (see sections 4.2 and 6.6)**	**Pack sizes**
Comirnaty LP.8.1 30 micrograms/dose dispersion for injection	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.	Multidose (2.25 mL) vial (grey cap)	6 doses of 0.3 mL	10 vials
Comirnaty LP.8.1 10 micrograms/dose dispersion for injection	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.	Single dose vial (blue cap)	1 dose of 0.3 mL	10 vials
		Multidose (2.25 mL) vial (blue cap)	6 doses of 0.3 mL	10 vials

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The storage and handling conditions printed on the vial or carton labels may differ from those in this product information. In these circumstances, the conditions in the product information should be followed.

Handling instructions prior to use

Comirnaty LP.8.1 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

Instructions applicable to single dose and multidose vials

- **Verify** that the vial has either:
  - a **grey plastic cap** and the product name is **Comirnaty LP.8.1 30 micrograms/dose dispersion for injection** (12 years and older), or
  - a **blue plastic cap** and the product **name is Comirnaty LP.8.1 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 WHO Product Information for that formulation.

Frozen vials
- 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.
  - Single dose vials: A 10-vial pack of single dose vials may take 2 hours to thaw.
  - Multidose vials: A 10-vial pack of multidose vials may take 6 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).
- Thawed vials can be handled in room light conditions.

Refrigerated only vials
- Unopened vials are stored at 2 °C to 8 °C; not exceeding the printed expiry date (EXP).
- The 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 dispersion may contain white to off-white opaque amorphous particles.
- After mixing, the vaccine should present as a:
  - **Grey cap:** white to off-white dispersion with no particulates visible.
  - **Blue cap:** clear to slightly opalescent dispersion with no particulates visible.
- Do not use the vaccine if particulates or discolouration are present.
- Check whether the vial is a single dose vial or a multidose vial and follow the applicable handling instructions below:
  - Single dose vials
    - Withdraw a single 0.3 mL dose of vaccine.
    - Discard vial and any excess volume.
  - Multidose vials
    - Multidose vials contain 6 doses of 0.3 mL each.
    - Using aseptic technique, cleanse the vial stopper with a single use antiseptic swab.
    - Withdraw 0.3 mL of Comirnaty LP.8.1.
    - **Low dead-volume syringes and/or needles** should be used in order to extract 6 doses from a single vial. The low dead-volume syringe and needle combination should have a dead-volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial.
    - Each dose must contain 0.3 mL of vaccine.
    - If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
    - Record the appropriate date/time on the multidose vial. Discard any unused vaccine 6 hours after first puncture.

Disposal

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

7. MANUFACTURER

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▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Comirnaty LP.8.1 3 micrograms/dose concentrate for dispersion for injection
COVID-19 mRNA Vaccine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

One vial (0.48 mL) contains 3 doses of 0.3 mL after dilution, see sections 4.2 and 6.6.

One dose (0.3 mL) contains 3 micrograms of mRNA encoding LP.8.1, a COVID-19 mRNA Vaccine (nucleoside modified, embedded in lipid nanoparticles).

The mRNA encoding LP.8.1 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 LP.8.1).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Comirnaty LP.8.1 concentrate for dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in infants and children aged 6 months to 4 years.

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

4.2 Posology and method of administration

Posology

Infants and children 6 months to 4 years of age without history of completion of a COVID-19 primary course or prior SARS-CoV-2 infection
Comirnaty LP.8.1 3 micrograms/dose concentrate for dispersion for injection is administered intramuscularly after dilution as a primary course of 3 doses. It is recommended to administer the second dose 3 weeks after the first dose followed by a third dose administered at least 8 weeks after the second dose (see sections 4.4 and 5.1).

If a child turns 5 years old between their doses in the primary course, he/she should complete the primary course at the same 3 micrograms dose level.

Infants and children 6 months to 4 years of age with history of completion of a COVID-19 primary course or prior SARS-CoV-2 infection
Comirnaty LP.8.1 3 micrograms/dose concentrate for dispersion for injection is administered intramuscularly after dilution as a single dose for infants and children 6 months to 4 years of age.

For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty LP.8.1 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Severely immunocompromised individuals
Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations (see section 4.4).

Interchangeability
The Comirnaty LP.8.1 3 micrograms/dose primary course may consist of any previous or current Comirnaty vaccine but not exceeding the total number of doses required as primary course. The primary course should only be administered once.

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

Paediatric population
There are paediatric formulations available for children 5 to 11 years of age. For details, please refer to the Summary of Product Characteristics 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 LP.8.1 concentrate for dispersion for injection should be administered intramuscularly after dilution (see section 6.6).

After dilution, vials with a **yellow cap** of Comirnaty LP.8.1 contain **3 doses of 0.3 mL** of vaccine. Standard syringes and needles can be used to extract 3 doses from a single vial. Irrespective of the type of syringe and needle:
- Each dose must contain **0.3 mL** of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of **0.3 mL**, discard the vial and any excess volume.
- Do not pool excess vaccine from multiple vials.

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

Do not inject the vaccine intravascularly, subcutaneously or intradermally.

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

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

For instructions regarding thawing, handling and disposal of the vaccine, see section 6.6.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Traceability

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

General recommendations

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

Close observation for at least 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
Safety and immunogenicity have been assessed in a limited number of immunocompromised individuals, including those receiving immunosuppressant therapy (see sections 4.8 and 5.1). The efficacy of Comirnaty LP.8.1 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 LP.8.1 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 LP.8.1 with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation

Comirnaty LP.8.1 3 micrograms/dose concentrate for dispersion for injection is not intended for individuals older than 5 years of age.

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

4.7 Effects on ability to drive and use machines

Comirnaty LP.8.1 has no or negligible influence on the ability to drive, cycle, and use machines. However, some of the effects mentioned under section 4.8 may temporarily affect the ability to drive, cycle, or use machines.

4.8 Undesirable effects

Summary of safety profile

The safety of Comirnaty LP.8.1 is inferred from safety data of the prior Comirnaty vaccines.

Initially approved Comirnaty vaccine
Infants 6 to 23 months of age – after 3 doses
In an analysis of Study 3 (Phase 2/3), 2 176 infants (1 458 initially approved Comirnaty 3 mcg and 718 placebo) were 6 to 23 months of age. Based on data in the blinded placebo-controlled follow-up period up to the cut-off date of 28 February 2023, 720 infants 6 to 23 months of age who received a 3-dose primary course (483 Comirnaty 3 mcg and 237 placebo) have been followed for a median of 1.7 months after the third dose.

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

Children 2 to 4 years of age – after 3 doses
In an analysis of Study 3 (Phase 2/3), 3 541 children (2 368 Comirnaty 3 mcg and 1 173 placebo) were 2 to 4 years of age. Based on data in the blinded placebo-controlled follow-up period up to the cut-off date of 28 February 2023, 1 268 children 2 to 4 years of age who received a 3-dose primary course (863 Comirnaty 3 mcg and 405 placebo) have been followed a median of 2.2 months after the third dose.

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

Children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after 2 doses
In Study 3, a total of 3 109 children 5 to 11 years of age received at least 1 dose of the initially approved Comirnaty vaccine and a total of 1 538 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, 2 206 (1 481 Comirnaty 10 mcg and 725 placebo) children have been followed for ≥ 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 (≥ 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 2 408 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, 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.

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 22 026 participants 16 years of age or older received at least 1 dose of Comirnaty 30 mcg 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.

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 ≥ 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.

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

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

Omicron-adapted Comirnaty
Infants 6 to 23 months of age – after the booster (fourth dose)
In 2 groups from Study 6 (Phase 3, Groups 2 and 3), 160 participants (Group 2: 92, Group 3: 68) 6 to 23 months of age who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (1.5/1.5 mcg) 2.1 to 8.6 months after receiving Dose 3 for Group 2 and 3.8 to 12.5 months after receiving Dose 3 for Group 3. Participants who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 had a median follow-up time of 4.4 months for Group 2 and had a median follow-up time of 6.4 months for Group 3.

The overall safety profile for the Comirnaty Original/Omicron BA.4-5 booster (fourth dose) was similar to that seen after 3 doses. The most frequent adverse reaction in participants 6 to 23 months of age was irritability (> 30%), decreased appetite (> 20%), drowsiness, tenderness at the injection site and fever (> 10%).

Children 2 to 4 years of age – after the booster (fourth dose)
In 2 groups from Study 6 (Phase 3, Groups 2 and 3), 1 207 participants (Group 2: 218, Group 3: 989) 2 to 4 years of age who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (1.5/1.5 mcg) 2.1 to 8.6 months after receiving Dose 3 for Group 2 and 2.8 to 17.5 months after receiving Dose 3 for Group 3. Participants who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 had a median follow-up time of 4.6 months for Group 2 and had a median follow-up time of 6.3 months for Group 3.

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

Children 5 to 11 years of age (i.e. 5 to less than 12 years of age) – after the booster (fourth dose)
In a subset from Study 6 (Phase 3), 113 participants 5 to 11 years of age who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (5/5 mcg) 2.6 to 8.5 months after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 had a median follow-up time of 6.3 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 myalgia (> 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%), myalgia (> 20%), chills (> 10%), and arthralgia (> 10%).

Participants 12 years of age and older – after a booster dose of Comirnaty Omicron XBB.1.5 (fourth dose or more)
In a subset from Study 13 (Phase 2/3), 412 participants 12 years of age and older, who had received at least 3 doses of an authorised mRNA COVID-19 vaccine, received a booster (fourth dose or more) of Comirnaty Omicron XBB.1.5 2.0 to 24.1 months after receiving Dose 3. Participants who received a booster (fourth dose or more) of Comirnaty XBB.1.5 had a median follow-up time of 6.3 months.

The safety profile of Comirnaty Omicron XBB.1.5 was similar to the overall Comirnaty safety profile.

Participants 12 years of age and older – after a single dose of Comirnaty Omicron XBB.1.5
In a subset from Study 13 (Phase 2/3), 311 participants 12 years of age and older who were considered to be baseline SARS-CoV-2 positive and COVID-19 vaccine-naïve, received 1 dose of Comirnaty Omicron XBB.1.5. Participants had a median follow-up time of 6.4 months.

The safety profile of Comirnaty Omicron XBB.1.5 was similar to the overall Comirnaty safety profile. The most frequent adverse reactions in participants were injection site pain (> 50%), fatigue (> 30%), headache (> 20%), myalgia, diarrhoea, arthralgia, chills and injection site swelling (> 10%).

Participants 12 years of age and older – after a single dose of Comirnaty Omicron JN.1
In a subset from Study 13 (Phase 2/3), 216 participants 12 years of age and older received 1 dose of Comirnaty Omicron JN.1 and had a median follow-up time of 6.3 months.

The safety profile of Comirnaty Omicron JN.1 was similar to the overall Comirnaty safety profile. The most frequent adverse reactions in participants were injection site pain (> 60%), fatigue (> 30%), headache (>20%), myalgia, chills and injection site swelling (> 10%).

Participants 18 years of age and older – after a single dose of Comirnaty Omicron KP.2
In a subset from Study 13 (Phase 2/3), 102 participants 18 years of age and older received 1 dose of Comirnaty Omicron KP.2 and had a median follow-up time of 6.3 months.

The safety profile of Comirnaty Omicron KP.2 was similar to the overall Comirnaty safety profile. The most frequent adverse reactions in participants were injection site pain (> 50%), fatigue (> 40%), headache and myalgia (> 20%).

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

Adverse reactions observed during clinical studies and post-authorisation experience 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 6 months of age and older

System Organ Class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Common	Lymphadenopathy[a]
Immune system disorders	Uncommon	Hypersensitivity reactions (e.g. rash[i], pruritus, urticaria, angioedema[b])
	Not known	Anaphylaxis
Metabolism and nutrition disorders	Uncommon	Decreased appetite[j]
Psychiatric disorders	Very common	Irritability[k]
	Uncommon	Insomnia
Nervous system disorders	Very common	Headache; drowsiness[k]
	Uncommon	Dizziness[d]; lethargy
	Rare	Acute peripheral facial paralysis[c]
	Not known	Paraesthesia[d]; hypoaesthesia[d]
Cardiac disorders	Very rare	Myocarditis[d]; pericarditis[d]
Gastrointestinal disorders	Very common	Diarrhoea[d]
	Common	Nausea; vomiting[d,m]
Skin and subcutaneous tissue disorder	Uncommon	Hyperhidrosis; night sweats
	Not known	Erythema multiforme[d]
Musculoskeletal and connective tissue disorders	Very common	Arthralgia; myalgia
	Uncommon	Pain in extremity[e]
Reproductive system and breast disorders	Not known	Heavy menstrual bleeding[l]
General disorders and administration site conditions	Very common	Injection site pain; injection site tenderness[k]; fatigue; chills; pyrexia[f]; injection site swelling
	Common	Injection site redness[h]
	Uncommon	Asthenia; malaise; injection site pruritus
	Not known	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 angioedema was rare.
c. Through the clinical trial safety follow-up period to 14 November 2020, acute peripheral facial paralysis (or palsy) was reported by four participants in the COVID-19 mRNA Vaccine group. Onset was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.
d. Adverse reaction determined post-authorisation.
e. Refers to vaccinated arm.
f. A higher frequency of pyrexia was observed after the second dose compared to the first dose.
g. Facial swelling in vaccine recipients with a history of injection of dermatological fillers has been reported in the post-marketing phase.
h. Injection site redness occurred at a higher frequency (very common) in participants 6 months to 11 years of age and in immunocompromised participants 2 years of age and older.
i. The frequency category for rash was common in participants 6 to 23 months of age.
j. The frequency category for decreased appetite was very common in participants 6 to 23 months of age.
k. Irritability, injection site tenderness, and drowsiness pertain to participants 6 to 23 months of age.

l. Most cases appeared to be non-serious and temporary in nature.
m. The frequency category for vomiting was very common in pregnant women 18 years of age and older and in immunocompromised participants 2 to 18 years of age.

Special populations

Infants born to pregnant participants – after 2 doses of Comirnaty
Study C4591015 (Study 9), a Phase 2/3, placebo-controlled study, evaluated a total of 346 pregnant participants who received Comirnaty (n = 173) or placebo (n = 173). Infants (Comirnaty n = 167 or placebo n = 168) were evaluated up to 6 months. No safety concerns were identified that were attributable to maternal vaccination with Comirnaty.

Immunocompromised participants (adults and children)
In study C4591024 (Study 10), a total of 124 immunocompromised participants 2 years of age and older received Comirnaty (see section 5.1).

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 via the national reporting system.

4.9 Overdose

There have been reports of higher than recommended doses of Comirnaty in clinical trials and post-authorisation experience. In general, adverse events reported with overdoses have been similar to the known adverse reaction profile of Comirnaty.

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 infants and children 6 months to 4 years of age – after the booster (fourth dose) with Comirnaty and Comirnaty Original/Omicron BA.4-5
In an analysis of a subset from Study 6, 310 participants 6 months to 4 years of age received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (1.5/1.5 mcg) after receiving 3 prior doses of Comirnaty 3 micrograms dose concentrate for dispersion. Results include immunogenicity data from a comparator subset of participants 6 months to 4 years of age in Study 3 who received 3 doses of Comirnaty 3 micrograms dose concentrate for dispersion.

Analyses of NT50 against Omicron BA.4-5 and against reference strain among participants 6 months to 5 years of age who received Comirnaty (Bivalent BA.4-5) as a booster dose in Study 6 compared to a subset of participants from Study 3 who received 3 doses of Comirnaty demonstrated superiority of anti-Omicron BA.4-5 response based on GMR and noninferiority based on difference in seroresponse rates, and noninferiority of anti-reference strain immune response based on GMR and difference in seroresponse rates (Table 2).

Table 2. Substudy B group 2 – Geometric mean ratios and difference in percentages of participants with seroresponse (1 month after dose 4 study 6/1 month after dose 3 study 3) - participants with or without evidence of infection - 6 months to 4 years of age - evaluable immunogenicity population

Geometric mean ratios (1 month after dose 4 study 6/1 month after dose 3 study 3)					
	Comirnaty (Bivalent BA.4-5) (3 mcg) Study 6		Comirnaty (3 mcg) Subset of Study 3		Comirnaty (Bivalent BA.4-5) (3 mcg) / Comirnaty (3 mcg)
Assay[f]	n[a]	GMT[b] (95% CI[b])	n[a]	GMT[b] (95% CI[b])	GMR[c] (95% CI)[c]
SARS-CoV-2 neutralisation assay - Omicron BA.4-5 - NT50 (titre)	223	1 839.3 (1 630.5, 2 074.9)	238	941.0 (838.1,1 058.2)	1.95 (1.65, 2.31)[d]
SARS-CoV-2 neutralisation assay – reference strain - NT50 (titre)	223	6 636.3 (6 017.5, 7 318.8)	238	7 305.4 (6 645.5, 8 030.7)	0.91 (0.79, 1.04)[e]

Difference in percentages of participants with seroresponse (1 month after dose 4 study 6/1 month after dose 3 study 3)					
Assay[f]	**Comirnaty (Bivalent BA.4-5) (3 mcg) Study 6**		**Comirnaty (3 mcg) Subset of Study 3**		**Difference**
	N[g]	**n[h] (%) (95% CI[i])**	**N[g]**	**n[h] (%) (95% CI[i])**	**%[j] (95% CI[k])**
SARS-CoV-2 neutralisation assay - Omicron BA.4-5 - NT50 (titre)	223	149 (66.8) (60.2, 73.0)	238	120 (50.4) (43.9, 56.9)	19.99 (11.61, 28.36)[l]
SARS-CoV-2 neutralisation assay – reference strain – NT50 (titre)	223	110 (49.3) (42.6, 56.1)	238	141 (59.2) (52.7, 65.5)	-0.15 (-7.79, 7.48)[m]

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

Note: Seroresponse is defined as achieving a ≥ 4-fold rise from baseline (before the first dose of study vaccination). If the baseline measurement is below the LLOQ, the post-vaccination measure of ≥ 4 × LLOQ is considered 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 CIs were calculated by exponentiating the LSMeans 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, age group (for ≥ 6 Months to < 5 Years only) and vaccine group as covariates. Assay results below the LLOQ were set to 0.5 × LLOQ.
c. GMRs and 2-sided CIs were calculated by exponentiating the difference of LSMeans for the assay and the corresponding CIs based on the same regression model as stated above.
d. Superiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 1.
e. 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.
f. 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).
g. 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. These values are the denominators for the percentage calculations.
h. n = Number of participants with seroresponse for the given assay at the given sampling time point.
i. Exact 2-sided CI based on the Clopper and Pearson method.
j. Adjusted difference in proportions, based on the Miettinen and Nurminen stratified by baseline neutralising titre category (< median, ≥ median), expressed as a percentage Comirnaty (Bivalent BA.4-5) [3 mcg] – Comirnaty [3 mcg]. The median of baseline neutralising titres was calculated based on the pooled data in 2 comparator groups.
k. 2-sided CI based on the Miettinen and Nurminen method for the difference in proportions stratified by baseline neutralising titre category (< median, ≥ median), expressed as a percentage.
l. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is > -5%.
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%.

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 3.

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

SARS-CoV-2 neutralisation assay	Sampling time point[a]	Vaccine group (as assigned/randomised)				
		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[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])	GMR[d] (95% CI[d])
Omicron BA.4-5 - NT50 (titre)[e]	Pre-vaccination	102	488.3 (361.9, 658.8)	112	248.3 (187.2, 329.5)	-
	1 month	102	2 189.9 (1 742.8, 2 751.7)	113	1 393.6 (1 175.8, 1 651.7)	1.12 (0.92, 1.37)
Reference strain - NT50 (titre)[e]	Pre-vaccination	102	2 904.0 (2 372.6, 3 554.5)	113	1 323.1 (1 055.7, 1 658.2)	-
	1 month	102	8 245.9 (7 108.9, 9 564.9)	113	7 235.1 (6 331.5, 8 267.8)	-

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 × 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 vaccine-naïve participants 12 years of age and older – after a single dose of Comirnaty Omicron XBB.1.5

In an analysis of a subset from Study 13, 302 vaccine-naïve participants 12 years of age and older who were considered to be SARS-CoV-2 positive at baseline and who received 1 dose of Comirnaty Omicron XBB.1.5 were compared to participants who received Comirnaty Omicron XBB.1.5 after at least 3 doses of an mRNA COVID-19 vaccine. The evaluable immunogenicity population who were vaccine-naïve had a median age of 36.0 years and comprised of 62.6% White and 50.7% Hispanic/Latino participants. The evaluable immunogenicity population who were vaccine-experienced (n=296) had a median age of 55 years and comprised of 79.4% White and 18.6% Hispanic/Latino.

Neutralising titres against Omicron XBB.1.5 increased from baseline to 1 month after study vaccination and were greater in participants receiving Comirnaty Omicron XBB.1.5 as a single dose

compared with participants who received Comirnaty Omicron XBB.1.5 after at least 3 doses of an mRNA COVID-19 vaccine. Noninferiority was met with respect to the geometric mean ratio (GMR) of Omicron XBB.1.5-neutralising titres, and the difference in seroresponse to the XBB.1.5 strain in vaccine-naïve participants compared to participants who received Comirnaty Omicron XBB.1.5 after at least 3 doses of an mRNA COVID-19 vaccine (Table 4).

Table 4. Geometric mean ratio and difference in percentages of participants with seroresponse – Study 13 vaccine-naïve and subset of vaccine-experienced – evaluable immunogenicity population

		Vaccine group (as assigned)				Group comparison	
		Vaccine-naïve Comirnaty Omicron XBB.1.5 30 mcg		Vaccine-experienced Comirnaty Omicron XBB.1.5 30 mcg		Vaccine-naïve Comirnaty Omicron XBB.1.5 30 mcg / Vaccine-experienced Comirnaty Omicron XBB.1.5 30 mcg	
SARS-CoV-2 neutralisation assay Omicron XBB.1.5 - NT50 (titre)[e]	**Sampling time point[a]**	**n[b]**	**GMT[c] (95% CI[c])**	**n[b]**	**GMT[c] (95% CI[c])**	**GMR[d] (95% CI[d])**	
Geometric mean 50% neutralising titre (GMT)	1 month	299	4 373.4 (3 757.1, 5 090.9)	296	2 915.7 (2 462.4, 3 452.5)	1.93 (1.52, 2.44)[f]	
	Sampling time point[a]	**N[g]**	**n[h] (%) (95% CI[i])**	**N[g]**	**n[h] (%) (95% CI[i])**	**Difference %[j]**	**(95% CI[k])**
Seroresponse rate (%) for 50% neutralising titre	1 month	298	253 (84.9) (80.3, 88.8)	295	218 (73.9) (68.5, 78.8)	7.31	(1.34, 13.28)[l]

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 both the pre−vaccination time point and 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. GMRs and the corresponding 2-sided 95% CIs were calculated by exponentiating the difference in least square means and the corresponding CIs based on a linear regression model with baseline assay results (log scale), age, and vaccine group as covariates.
e. SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (Omicron subvariant XBB.1.5).
f. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67.
g. 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. These values are the denominators for the percentage calculations.
h. n = Number of participants with a seroresponse for the given assay at the given sampling time point.
i. Exact 2-sided CI, based on the Clopper and Pearson method.
j. Difference in proportions, expressed as a percentage.
k. 2-Sided CI, based on the Miettinen and Nurminen method stratified by baseline neutralising titre category (< median, ≥ median) and age group (< median, ≥ median). The median of baseline neutralising titres and median age was calculated based on the pooled data in 2 comparator groups.
l. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is > -10%.

Immunogenicity in participants 12 years of age and older – after a single dose of Comirnaty Omicron JN.1

In an analysis of a subset from Study 13, 212 participants 12 years of age and older who received 1 dose of Comirnaty Omicron JN.1 were compared to 200 participants who received Comirnaty Omicron XBB.1.5 after receiving at least 3 doses of an mRNA COVID-19 vaccine. The evaluable immunogenicity population who received Comirnaty Omicron JN.1 had a median age of 54.5 years

and comprised of 69.3% White and 23.1% Hispanic/Latino participants, and 87.3% were positive for SARS-CoV-2 at baseline, and 89.2% had previously received a COVID-19 vaccine.

Neutralising titres and seroresponse against Omicron JN.1 or Omicron XBB.5 in participants receiving Comirnaty Omicron JN.1 or Comirnaty Omicron XBB.1.5 are presented in Table 5.

Table 5. Geometric mean titres and percentage of participants achieving seroresponse – Comirnaty JN.1 or Comirnaty XBB.1.5 – participants 12 years of age and older – evaluable immunogenicity population

		Comirnaty Omicron JN.1 30 mcg		Comirnaty Omicron XBB.1.5 30 mcg	
Geometric mean 50% neutralising titre (GMT)	**Sampling time point[a]**	**n[b]**	**GMT[c] (95% CI[c])**	**n[b]**	**GMT[c] (95% CI[c])**
SARS-CoV-2 neutralisation assay – Omicron JN.1 - NT50 (titre)[d]	Pre-vaccination	211	190.4 (153.6, 235.9)	198	155.5 (126.6, 190.8)
	1 month	212	2203.3 (1855.7, 2616.0)	199	1133.8 (950.7, 1352.2)
SARS-CoV-2 neutralisation assay – Omicron XBB.1.5 – NT50 (titre)[e]	Pre-vaccination	212	290.3 (233.0, 361.6)	200	219.2 (177.5, 270.7)
	1 month	212	2364.4 (1917.4, 2915.6)	200	2848.1 (2341.9, 3463.8)
Seroresponse rate for 50% neutralising titre	**Sampling time point[a]**	**N[f]**	**n[g] (%) (95% CI[h])**	**N[b]**	**n[g] (%) (95% CI[h])**
SARS-CoV-2 neutralisation assay – Omicron JN.1 - NT50 (titre)[d]	1 month	211	149 (70.6) (64.0, 76.7)	197	129 (65.5) (58.4, 72.1)
SARS-CoV-2 neutralisation assay – Omicron XBB.1.5 – NT50 (titre)[e]	1 month	212	128 (60.4) (53.5, 67.0)	200	164 (82.0) (76.0, 87.1)

Abbreviations: 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 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 (Omicron subvariant JN.1).
e. SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (Omicron subvariant XBB.1.5).
f. 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. These values are the denominators for the percentage calculations.
g. n = Number of participants with a seroresponse for the given assay at the given sampling time point.
h. Exact 2-sided CI, based on the Clopper and Pearson method.

Immunogenicity in participants 12 years of age and older – after a single dose of Comirnaty Omicron KP.2

In an analysis of a subset from Study 13, 100 participants 18 years of age and older who received 1 dose of Comirnaty Omicron KP.2 were compared to 194 participants who received 1 dose of Comirnaty Omicron JN.1. The evaluable immunogenicity population who received Comirnaty Omicron KP.2 had a median age of 55.0 years and comprised of 75.0% White and 15.0% Hispanic/Latino participants, 91.0% were positive for SARS-CoV-2 at baseline, and 90.0% had previously received a COVID-19 vaccine.

Neutralising titres and seroresponse against Omicron KP.2 and Omicron JN.1 in participants receiving Comirnaty Omicron KP.2 or Comirnaty Omicron JN.1 are presented in Table 6.

Table 6. Geometric mean titres and percentage of participants achieving seroresponse – Comirnaty KP.2 or Comirnaty JN.1 – participants 18 years of age and older – evaluable immunogenicity population

		Comirnaty Omicron KP.2 30 mcg		Comirnaty Omicron JN.1 30 mcg	
Geometric mean 50% neutralising titre (GMT)	**Sampling time point[a]**	**n[b]**	**GMT[c] (95% CI[c])**	**n[b]**	**GMT[c] (95% CI[c])**
SARS-CoV-2 neutralisation assay – Omicron KP.2 – NT50 (titre)[d]	Pre-vaccination	99	207.6 (150.0, 287.4)	194	78.3 (64.2, 95.6)
	1 month	100	2256.5 (1660.2, 3067.0)	194	873.3 (706.1, 1080.2)
SARS-CoV-2 neutralisation assay – Omicron JN.1 – NT50 (titre)[e]	Pre-vaccination	100	492.5 (359.8, 674.0)	194	185.1 (148.1, 231.4)
	1 month	100	4319.5 (3280.7, 5687.2)	194	2088.6 (1743.9, 2501.5)
Seroresponse rate for 50% neutralising titre	**Sampling time point[a]**	**N[f]**	**n[g] (%) (95% CI[h])**	**N[b]**	**n[g] (%) (95% CI[h])**
SARS-CoV-2 neutralisation assay – Omicron KP.2 – NT50 (titre)[d]	1 month	99	76 (76.8) (67.2, 84.7)	194	130 (67.0) (59.9, 73.6)
SARS-CoV-2 neutralisation assay – Omicron JN.1 – NT50 (titre)[e]	1 month	100	64 (64.0) (53.8, 73.4)	194	137 (70.6) (63.7, 76.9)

Abbreviations: 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 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 (Omicron subvariant KP.2).
e. SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (Omicron subvariant JN.1).
f. 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. These values are the denominators for the percentage calculations.
g. n = Number of participants with a seroresponse for the given assay at the given sampling time point.
h. Exact 2-sided CI, based on the Clopper and Pearson method.

Comirnaty

Study 2 is a multicentre, multinational, Phase 1/2/3 randomised, placebo-controlled, observer-blind dose-finding, vaccine candidate selection and efficacy study in participants 12 years of age and older. Randomisation was stratified by age: 12 to 15 years of age, 16 to 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥ 56-year stratum. The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19. Participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalisation 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/m^2, chronic pulmonary disease, diabetes mellitus, hypertension).

The vaccine efficacy information is presented in Table 7.

Table 7. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of 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 2.214 (17 411)	162 2.222 (17 511)	95.0 (90.0, 97.9)
16 to 64 years	7 1.706 (13 549)	143 1.710 (13 618)	95.1 (89.6, 98.1)
65 years and older	1 0.508 (3 848)	19 0.511 (3 880)	94.7 (66.7, 99.9)
65 to 74 years	1 0.406 (3 074)	14 0.406 (3 095)	92.9 (53.1, 99.8)
75 years and older	0 0.102 (774)	5 0.106 (785)	100.0 (-13.1, 100.0)

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

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

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 8.

Table 8. 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 6.247 (20 712)	850 6.003 (20 713)	91.3 (89.0, 93.2)
16 to 64 years	70 4.859 (15 519)	710 4.654 (15 515)	90.6 (87.9, 92.7)
65 years and older	7 1.233 (4 192)	124 1.202 (4 226)	94.5 (88.3, 97.8)
65 to 74 years	6 0.994 (3 350)	98 0.966 (3 379)	94.1 (86.6, 97.9)
75 years and older	1 0.239 (842)	26 0.237 (847)	96.2 (76.9, 99.9)

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

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

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 9) 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 9. 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 8.439[e] (22 505)	30 8.288[e] (22 435)	96.7 (80.3, 99.9)
7 days after Dose 2[f]	1 6.522[g] (21 649)	21 6.404[g] (21 730)	95.3 (70.9, 99.9)

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, non−invasive 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.

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 10. 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 10. 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

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*			
	COVID-19 mRNA Vaccine 10 mcg/dose N[a]=1 305 Cases n1[b] Surveillance time[c] (n2[d])	**Placebo N[a]=663 Cases n1[b] Surveillance time[c] (n2[d])**	**Vaccine efficacy % (95% CI)**
Children 5 to 11 years of age	3 0.322 (1 273)	16 0.159 (637)	90.7 (67.7, 98.3)

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

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

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

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

c. Total surveillance time in 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.

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 2 703 participants who received the vaccine and 42 cases out of 1 348 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 3 018 who received vaccine and 42 cases in 1 511 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 pre-specified 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 11.

Table 11. 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			
		10 mcg/dose 5 to 11 years N[a]=264	30 mcg/dose 16 to 25 years N[a]=253	5 to 11 years/ 16 to 25 years	
	Time point[b]	GMT[c] (95% CI[c])	GMT[c] (95% CI[c])	GMR[d] (95% CI[d])	Met immunobridging objective[e] (Y/N)
Geometric mean 50% neutralising titre[f] (GMT[c])	1 month after Dose 2	1 197.6 (1 106.1, 1 296.6)	1 146.5 (1 045.5, 1 257.2)	1.04 (0.93, 1.18)	Y
	Time point[b]	**n[g] (%) (95% CI[h])**	**n[g] (%) (95% CI[h])**	**Difference %[i] (95% CI[j])**	**Met immunobridging objective[k] (Y/N)**
Seroresponse rate (%) for 50% neutralising titre[f]	1 month after Dose 2	262 (99.2) (97.3, 99.9)	251 (99.2) (97.2, 99.9)	0.0 (-2.0, 2.2)	Y

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

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

Note: Seroresponse is defined as achieving a ≥ 4-fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a post-vaccination assay result ≥ 4 × 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 × 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 ≥ 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 to 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 summarised in Table 12.

Table 12. Summary of geometric mean titres – NT50 – participants without evidence of infection – phase 2/3 – immunogenicity set – 5 to 11 years of age – evaluable immunogenicity population

	Sampling time point[a]		
Assay	**1 month after booster dose (n[b]=67) GMT[c] (95% CI[c])**	**1 month after dose 2 (n[b]=96) GMT[c] (95% CI[c])**	**1 month after booster dose/ 1 month after dose 2 GMR[d] (95% CI[d])**
SARS-CoV-2 neutralisation assay - NT50 (titre)	2 720.9 (2 280.1, 3 247.0)	1 253.9 (1 116.0, 1 408.9)	2.17 (1.76, 2.68)

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

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 × 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).

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

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

The vaccine efficacy results after Dose 3 in participants 6 months to 4 years of age are presented in Table 13.

Table 13. Vaccine efficacy – first COVID-19 occurrence from 7 days after Dose 3 – blinded follow-up period – participants without evidence of infection prior to 7 days after Dose 3 – phase 2/3 – 6 months to 4 years of age – evaluable efficacy (3-dose) population

First COVID-19 occurrence from 7 days after Dose 3 in participants without evidence of prior SARS-CoV-2 infection*			
Subgroup	COVID-19 mRNA Vaccine 3 mcg/Dose N[a]=873 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=381 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI[e])
6 months to 4 years[e]	13 0.124 (794)	21 0.054 (351)	73.2 (43.8, 87.6)
2 to 4 years	9 0.081 (498)	13 0.033 (204)	71.8 (28.6, 89.4)
6 months to 23 months	4 0.042 (296)	8 0.020 (147)	75.8 (9.7, 94.7)

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

* Participants who had no serological or virological evidence (prior to 7 days after receipt of Dose 3) of past SARS-CoV-2 infection (i.e. negative N-binding antibody [serum] result at Dose 1, 1 month post-Dose 2 (if available), Dose 3 (if available) visits, SARS-CoV-2 not detected by NAAT [nasal swab] at Dose 1, Dose 2, and Dose 3 study visits, and a negative NAAT [nasal swab] result at any unscheduled visit prior to 7 days after receipt of Dose 3) and had no medical history of COVID-19 were included in the analysis.

a. N = number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 3 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Two-sided 95% confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.

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

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

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

SARS-CoV-2 50% neutralising antibody titres (NT50) were compared between an immunogenicity subset of Phase 2/3 participants 6 to 23 months of age and 2 to 4 years of age from Study 3 at 1 month after the 3-dose primary course and a randomly selected subset from Study 2 Phase 2/3 participants 16 to 25 years of age at 1 month after the 2-dose primary course, using a microneutralisation assay against the reference strain (USA_WA1/2020).

The primary immunobridging analyses compared the geometric mean titres (using a geometric mean ratio [GMR]) and the seroresponse (defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from before Dose 1) rates in the evaluable immunogenicity population of participants without evidence of prior SARS-CoV-2 infection up to 1 month after Dose 3 in participants 6 to 23 months of age and 2 to 4 years of age and up to 1 month after Dose 2 in participants 16 to 25 years of age. The

pre-specified immunobridging criteria were met for both the GMR and the seroresponse difference for both age groups (Table 14).

Table 14. SARS-CoV-2 GMTs (NT50) and difference in percentages of participants with seroresponse at 1 month after vaccination course – immunobridging subset - participants 6 months to 4 years of age (Study 3) 1 month after Dose 3 and participants 16 to 25 years of age (Study 2) 1 month after Dose 2 – without evidence of SARS-CoV-2 infection – evaluable immunogenicity population

SARS-CoV-2 GMTs (NT50) at 1 month after vaccination course							
SARS-CoV-2 neutralisation assay - NT50 (titre)[e]							
Age	**N[a]**	**GMT[b] (95% CI[b]) (1 month after Dose 3)**	**Age**	**N[a]**	**GMT[b] (95% CI[b]) (1 month after Dose 2)**	**Age**	**GMR[c,d] (95% CI)**
2 to 4 years	143	1 535.2 (1 388.2, 1 697.8)	16 to 25 years of age	170	1 180.0 (1 066.6, 1 305.4)	2 to 4 years/16 to 25 years of age	1.30 (1.13, 1.50)
6 to 23 months	82	1 406.5 (1 211.3, 1 633.1)	16 to 25 years of age	170	1 180.0 (1 066.6, 1 305.4)	6 to 23 months years/16 to 25 years of age	1.19 (1.00, 1.42)
Difference in percentages of participants with seroresponse at 1 month after vaccination course							
SARS-CoV-2 neutralisation assay - NT50 (titre)[e]							
Age	**N[a]**	**n[f] (%) (95% CI[g]) (1 month after Dose 3)**	**Age**	**N[a]**	**n[f] (%) (95% CI[g]) (1 month after Dose 2)**	**Age**	**Difference in seroresponse rates %[h] (95% CI[i])[j]**
2 to 4 years	141	141(100.0) (97.4, 100.0)	16 to 25 years of age	170	168 (98.8) (95.8, 99.9)	2 to 4 years/16 to 25 years of age	1.2 (1.5, 4.2)
6 to 23 months	80	80 (100.0) (95.5, 100.0)	16 to 25 years of age	170	168 (98.8) (95.8, 99.9)	6 to 23 months years/16 to 25 years of age	1.2 (3.4, 4.2)

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

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

Note: Seroresponse is defined as achieving a ≥ 4-fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a post-vaccination 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 dose/sampling time point for GMTs and number of participants with valid and determinate assay results for the specified assay at both baseline and the given dose/sampling time point for seroresponse rates.
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 mean difference of the logarithms of the titres (younger age group minus 16 to 25 years of age) and the corresponding CI (based on the Student t distribution).
d. For each younger age group (2 to 4 years, 6 to 23 months), immunobridging based on GMR is declared if the lower bound of the 2-sided 95% CI for the GMR ratio is greater than 0.67 and the point estimate of the GMR is ≥ 0.8.
e. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralisation Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus 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.
f. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.
g. Exact 2-sided CI based on the Clopper and Pearson method.
h. Difference in proportions, expressed as a percentage (younger age group minus 16 to 25 years of age).
i. 2-sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
j. For each younger age group (2 to 4 years, 6 to 23 months), immunobridging based on seroresponse rate is declared if the lower bound of the 2-sided 95% CI for the difference in proportions is greater than -10.0% provided that the immunobridging criteria based on GMR were met.

Immunogenicity in immunocompromised participants (adults and children)
Study 10 is a Phase 2b, open-label study (n = 124) that enrolled immunocompromised participants 2 to < 18 years of age receiving immunomodulator therapy or who have undergone solid organ transplant (within the previous 3 months) and are on immunosuppression or who have undergone bone marrow or stem cell transplant at least 6 months prior to enrolment and in immunocompromised participants 18 years of age and older treated for non-small cell lung cancer (NSCLC) or chronic lymphocytic leukaemia (CLL), receiving haemodialysis for secondary to end-stage renal disease, or receiving immunomodulator therapy for an autoimmune inflammatory disorder. Participants received 4 age-appropriate doses of Comirnaty (3 mcg, 10 mcg, or 30 mcg); the first 2 doses separated by 21 days, with the third dose occurring 28 days after the second dose, followed by a fourth dose, 3 to 6 months after Dose 3.

Analysis of immunogenicity data at 1 month after Dose 3 (26 participants 2 to < 5 years of age, 56 participants 5 to < 12 years of age, 11 participants 12 to < 18 years of age, and 4 participants ≥ 18 years of age) and 1 month after Dose 4 (16 participants 2 to < 5 years of age, 31 participants 5 to < 12 years of age, 6 participants 12 to < 18 years of age, and 4 participants ≥ 18 years of age) in the evaluable immunogenicity population without evidence of prior infection demonstrated a vaccine-elicited immune response. GMTs were observed to be substantially higher at 1 month after Dose 3 and further increased at 1 month after Dose 4 and remained high at 6 months after Dose 4 compared to levels observed before study vaccination across age groups and disease subsets.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Comirnaty in one or more subsets of the paediatric population in prevention of COVID-19 (see section 4.2 for information on paediatric use).

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 post-natal day 21 as well as in foetuses and offspring. There were no vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development. No Comirnaty data are available on vaccine placental transfer or excretion in milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

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

6.3 Shelf life

The storage and handling conditions printed on the vial or carton labels may differ from those in this product information. In these circumstances, the conditions in the product information should be followed.

Unopened vials

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.

18 months when stored at -90 °C to -60 °C.
Within the 18-month shelf life the thawed (previously frozen) vials may be stored at 2 °C to 8 °C for up to 10 weeks.

Thawing procedure
When stored frozen at -90 °C to -60 °C, 10-vial packs of the vaccine can be thawed at 2 °C to 8 °C for 2 hours.

Thawed (previously frozen) vials
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.

Thawed vials can be handled in room light conditions.

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

Opened vial

Once the vaccine vial is diluted, it should be used immediately or within 6 hours and kept at 2 °C to 8 °C.

6.4 Special precautions for storage

Store in a freezer at -90 °C to -60 °C.
Store in the original package in order to protect from light.
During storage, minimise exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.

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

6.5 Nature and contents of container

0.48 mL concentrate for dispersion in a 2 mL clear multidose vial (type I glass) with a stopper (synthetic bromobutyl rubber) and a yellow flip-off plastic cap with aluminium seal. Each vial contains 3 doses, see section 6.6.

Pack size: 10 vials

6.6 Special precautions for disposal and other handling

The storage and handling conditions printed on the vial or carton labels may differ from those in this product information. In these circumstances, the conditions in the product information should be followed.

Handling instructions prior to use

Comirnaty LP.8.1 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- **Verify** that the vial has a **yellow plastic cap** and the product **name is Comirnaty LP.8.1 3 micrograms/dose concentrate for dispersion for injection** (infants and children 6 months to 4 years).
- If the vial has another product name on the label, or a different cap colour, please make reference to the WHO Product Information for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 10-vial pack may take 2 hours to thaw. Ensure vials are completely thawed prior to use.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).

- Thawed vials can be handled in room light conditions.

Dilution

- Allow the thawed vial to come to room temperature and gently invert it 10 times prior to dilution. Do not shake.
- Prior to dilution, the thawed dispersion may contain white to off-white opaque amorphous particles.
- The thawed vaccine must be diluted in its original vial with **1.1 mL sodium chloride 9 mg/mL (0.9%) solution for injection**, using a 21 gauge or narrower needle and aseptic techniques.
- Equalise vial pressure before removing the needle from the vial stopper by withdrawing 1.1 mL air into the empty diluent syringe.
- Gently invert the diluted dispersion 10 times. Do not shake.
- The diluted vaccine should present as a clear to slightly opalescent dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discolouration are present.
- The diluted vials should be marked with the appropriate **discard date and time**.
- **After dilution**, store at 2 ºC to 8 ºC and use within **6 hours**.
- Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.

Preparation of **0.3 mL** doses

- After dilution, the vial contains 1.58 mL from which **3 doses** of **0.3 mL** can be extracted.
- Using aseptic technique, cleanse the vial stopper with a single use antiseptic swab.
- Withdraw **0.3 mL** of Comirnaty LP.8.1 for infants and children aged 6 months to 4 years. **Standard syringes and/or needles** can be used in order to extract 3 doses from a single vial.
- Each dose must contain **0.3 mL** of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of **0.3 mL**, discard the vial and any excess volume.
- Discard any unused vaccine within 6 hours after dilution.

Disposal

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

7. MANUFACTURER

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