

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

▼ 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 30 micrograms/dose concentrate for dispersion for injection
COVID-19 mRNA Vaccine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

One vial (0.45 mL) contains 6 doses of 0.3 mL after dilution, see sections 4.2 and 6.6.

One dose (0.3 mL) contains 30 micrograms of tozinameran, a COVID-19 mRNA Vaccine (nucleoside modified, embedded in lipid nanoparticles).

Tozinameran 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.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Comirnaty 30 micrograms/dose concentrate for dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 12 years of age and older.

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

4.2 Posology and method of administration

Posology

Individuals 12 years of age and older

Comirnaty is administered intramuscularly after dilution 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 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Severely immunocompromised aged 12 years and older

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

Paediatric population

There are paediatric formulations available for infants aged 6 months and above and children below 12 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.

Elderly population

No dose adjustment is required in elderly individuals ≥ 65 years of age.

Method of administration

Comirnaty 30 micrograms/dose concentrate for dispersion for injection should be administered intramuscularly after dilution (see section 6.6).

After dilution, vials of Comirnaty 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.

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, hypoesthesia and sweating) may occur in association with the vaccination process itself. Stress-related reactions are temporary and resolve on their own. Individuals should be advised to bring symptoms to the attention of the vaccination provider for evaluation. It is important that precautions are in place to avoid injury from fainting.

Concurrent illness

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

Thrombocytopenia and coagulation disorders

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

Immunocompromised individuals

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

Excipients

This vaccine contains less than 1 mmol potassium (39 mg) per dose, that is to say essentially 'potassium-free'.

This vaccine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

A large amount of observational data from pregnant women vaccinated with Comirnaty 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). Comirnaty can be used during pregnancy.

Breast-feeding

No effects on the breastfed newborn/infant are anticipated since the systemic exposure of breast-feeding woman to Comirnaty is negligible. Observational data from women who were breast-feeding after vaccination have not shown a risk for adverse effects in breastfed newborns/infants. Comirnaty 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 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

Participants 16 years of age and older – after 2 doses

In Study 2, a total of 22 026 participants 16 years of age or older received at least 1 dose of Comirnaty and a total of 22 021 participants 16 years of age or older received placebo (including 138 and 145 adolescents 16 and 17 years of age in the vaccine and placebo groups, respectively). A total of 20 519 participants 16 years of age or older received 2 doses of Comirnaty.

At the time of the analysis of Study 2 with a data cut-off of 13 March 2021 for the placebo-controlled blinded follow-up period up to the participants' unblinding dates, a total of 25 651 (58.2%) participants (13 031 Comirnaty and 12 620 placebo) 16 years of age and older were followed up for ≥ 4 months after the second dose. This included a total of 15 111 (7 704 Comirnaty and 7 407 placebo) participants 16 to 55 years of age and a total of 10 540 (5 327 Comirnaty and 5 213 placebo) participants 56 years of age and older.

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

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

Adolescents 12 to 15 years of age – after 2 doses

In an analysis of long-term safety follow-up in Study 2, 2 260 adolescents (1 131 Comirnaty and 1 129 placebo) were 12 to 15 years of age. Of these, 1 559 adolescents (786 Comirnaty and 773 placebo) have been followed for ≥ 4 months after the second dose of Comirnaty.

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

Participants 12 years of age and older – after booster dose

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 (see section 5.1).

Tabulated list of adverse reactions from clinical studies and post-authorisation experience in individuals 12 years of age and older

Adverse reactions observed during clinical studies are listed below according to the following frequency categories: Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1\ 000$ to $< 1/100$), Rare ($\geq 1/10\ 000$ to $< 1/1\ 000$), Very rare ($< 1/10\ 000$), Not known (cannot be estimated from the available data).

Table 1. Adverse reactions from Comirnaty clinical trials and post-authorisation experience in individuals 12 years of age and older

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
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 ^h
General disorders and administration site conditions	Very common	Injection site pain; fatigue; chills; pyrexia ^f ; injection site swelling
	Common	Injection site redness
	Uncommon	Asthenia; malaise; injection site pruritus
	Not known	Extensive swelling of vaccinated limb ^d ; facial swelling ^g

- In participants 5 years of age and older, a higher frequency of lymphadenopathy was reported after a booster ($\leq 2.8\%$) dose than after primary ($\leq 0.9\%$) doses of the vaccine.
- The frequency category for urticaria and angioedema was rare.
- Through the clinical trials safety follow-up period to 14 November 2020, acute peripheral facial paralysis (or palsy) was reported by four participants in the COVID-19 mRNA Vaccine group. Onset was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.
- Adverse reaction determined post-authorisation.
- Refers to vaccinated arm.
- A higher frequency of pyrexia was observed after the second dose compared to the first dose.
- Facial swelling in vaccine recipients with a history of injection of dermatological fillers has been reported in the post-marketing phase.
- Most cases appeared to be non-serious and temporary in nature.

Description of selected adverse reactions

Myocarditis and pericarditis

The increased risk of myocarditis after vaccination with Comirnaty is highest in younger males (see section 4.4).

Two large European pharmacoepidemiological studies have estimated the excess risk in younger males following the second dose of Comirnaty. One study showed that in a period of 7 days after the second dose there were about 0.265 (95% CI 0.255 - 0.275) extra cases of myocarditis in 12-29 year old males per 10 000 compared to unexposed persons. In another study, in a period of 28 days after the second dose there were 0.56 (95% CI 0.37 - 0.74) extra cases of myocarditis in 16-24 year old males per 10 000 compared to unexposed persons.

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#) and include batch/Lot number if available.

4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vaccines, viral vaccines, ATC code: J07BN01

Mechanism of action

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

Efficacy

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

significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrolment, were included as were participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis B virus (HBV).

Efficacy in participants 16 years of age and older – after 2 doses

In the Phase 2/3 portion of Study 2, based on data accrued through 14 November 2020, approximately 44 000 participants were randomised equally and were to receive 2 doses of 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) \geq 30 kg/m², chronic pulmonary disease, diabetes mellitus, hypertension).

The vaccine efficacy information is presented in Table 2.

Table 2. 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 n^{1b} Surveillance time^c (n2^d)	Placebo N^a = 18 325 Cases n^{1b} 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 3.

Table 3. 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.

- N = Number of participants in the specified group.
- n1 = Number of participants meeting the endpoint definition.
- 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.
- n2 = Number of participants at risk for the endpoint.
- Two-sided 95% confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
- Included confirmed cases in participants 12 to 15 years of age: 0 in the COVID-19 mRNA Vaccine group; 16 in the placebo group.

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

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

Efficacy against severe COVID-19

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

As of 13 March 2021, vaccine efficacy against severe COVID-19 is presented only for participants with or without prior SARS-CoV-2 infection (Table 4) 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 4. 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 $\leq 93\%$ on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen < 300 mm Hg);
- Respiratory failure [defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
- Evidence of shock (systolic blood pressure < 90 mm Hg, diastolic blood pressure < 60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an Intensive Care Unit;
- Death.

- n1 = Number of participants meeting the endpoint definition.
- n2 = Number of participants at risk for the endpoint.

- c. Two-side confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
- d. Efficacy assessed based on the Dose 1 all available efficacy (modified intention-to-treat) population that included all randomised participants who received at least 1 dose of study intervention.
- e. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.
- f. Efficacy assessed based on the evaluable efficacy (7 Days) population that included all eligible randomised participants who receive all dose(s) of study intervention as randomised within the predefined window, have no other important protocol deviations as determined by the clinician.
- g. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

Efficacy and immunogenicity in adolescents 12 to 15 years of age – after 2 doses

In an initial analysis of Study 2 in adolescents 12 to 15 years of age (representing a median follow-up duration of > 2 months after Dose 2) without evidence of prior infection, there were no cases in 1 005 participants who received the vaccine and 16 cases out of 978 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 75.3, 100.0). In participants with or without evidence of prior infection there were 0 cases in the 1 119 who received vaccine and 18 cases in 1 110 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 78.1, 100.0).

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

In the updated efficacy analysis of Study 2 in adolescents 12 to 15 years of age without evidence of prior infection, there were no cases in 1 057 participants who received the vaccine and 28 cases out of 1 030 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 86.8, 100.0) during the period when Alpha variant was the predominant circulating strain. In participants with or without evidence of prior infection there were 0 cases in the 1 119 who received vaccine and 30 cases in 1 109 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 87.5, 100.0).

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

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

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

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

Table 5. SARS-CoV-2 neutralization assay - NT50 (titre)[†] (SARS-CoV-2 USA_WA1/2020) – GMT and seroresponse rate comparison of 1 month after booster dose to 1 month after primary series – participants 18 through 55 years of age without evidence of infection up to 1 month after booster dose* – booster dose evaluable immunogenicity population[±]

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

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

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

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

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

a. n = Number of participants with valid and determinate assay results at both sampling time points within specified window.

b. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.

c. GMRs and 2-sided 97.5% CIs were calculated by exponentiating the mean differences in the logarithms of the assay and the corresponding CIs (based on the Student t distribution).

d. Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the GMR is > 0.67 and the point estimate of the GMR is ≥ 0.80 .

e. n = Number of participants with valid and determinate assay results for the specified assay at baseline, 1 month after Dose 2 and 1 month after the booster dose within specified window. These values are the denominators for the percentage calculations.

f. Number of participants with seroresponse for the given assay at the given dose/sampling time point. Exact 2-sided CI based on the Clopper and Pearson method.

g. Difference in proportions, expressed as a percentage (1 month after booster dose – 1 month after Dose 2).

h. Adjusted Wald 2-sided CI for the difference in proportions, expressed as a percentage.

i. Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the percentage difference is $> -10\%$.

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

An interim efficacy analysis of Study 4, a placebo-controlled booster study performed in approximately 10 000 participants 16 years of age and older who were recruited from Study 2, evaluated confirmed COVID-19 cases accrued from at least 7 days after booster vaccination up to a

data cut-off date of 5 October 2021, which represents a median of 2.5 months post-booster follow-up. The booster dose was administered 5 to 13 months (median 11 months) after the second dose. Vaccine efficacy of the Comirnaty booster dose after the primary series relative to the placebo booster group who only received the primary series dose was assessed.

The relative vaccine efficacy information for participants 16 years of age and older without prior evidence of SARS-CoV-2 infection is presented in Table 6. 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 6. 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.

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

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

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

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

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

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

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

In Substudy D [a subset from Study 2 (Phase 3) and Study 4 (Phase 3)], 325 participants 18 to ≤ 55 years of age who had completed 3 doses of Comirnaty received Comirnaty (30 mcg) as a booster dose (fourth dose) 90 to 180 days after receiving Dose 3. For the immunogenicity subset data see Table 7.

Table 7. Summary of immunogenicity data from participants in C4591031 Substudy D (cohort 2 full expanded set) and Substudy E (expanded cohort immunogenicity subset) who received Comirnaty 30 mcg as booster (fourth dose) – participants without evidence of infection up to 1 month after booster dose – evaluable immunogenicity population

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

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

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

Note: Substudy D Full Expanded Set = Cohort 2 excluding the sentinel group; Substudy E Immunogenicity Subset = a random sample of 230 participants in each vaccine group selected from the expanded cohort. Note: Participants who had no serological or virological evidence (prior to the 1-month post-study vaccination blood sample collection) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] result negative at the study vaccination and the 1-month post-study vaccination visits, negative NAAT [nasal swab] result at the study vaccination visit, and any unscheduled visit prior to the 1-month post-study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.

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

- a. Protocol-specified timing for blood sample collection.
- b. N = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- c. N = Number of participants with valid and determinate assay results for the specified assay at both the pre-vaccination time point and the given sampling time point.
- d. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
- e. n = Number of participants with seroresponse for the given assay at the given sampling time point.
- f. Exact 2-sided CI, based on the Clopper and Pearson method.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Comirnaty in 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 neutralizing antibody responses were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in foetuses and offspring. There were no vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development. No Comirnaty data are available on vaccine placental transfer or excretion in milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)
2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)
1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
Cholesterol
Potassium chloride
Potassium dihydrogen phosphate
Sodium chloride
Disodium phosphate dihydrate
Sucrose
Water for injections
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial

Frozen vial

2 years when stored at -90 °C to -60 °C.

Within the 2-year shelf life unopened vials may be stored and transported at -25 °C to -15 °C for a single period of up to 2 weeks and can be returned to -90 °C to -60 °C.

When stored frozen at -90 °C to -60 °C, 195-vial packs of the vaccine can be thawed at 2 °C to 8 °C for 3 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed vial

1 month at 2 °C to 8 °C within the 2-year shelf life.

Within the 1-month shelf life at 2 °C to 8 °C, up to 48 hours may be used for transportation.

Prior to use, the unopened vial can be stored for up to 2 hours at temperatures up to 30 °C.

Thawed vials can be handled in room light conditions.

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

Handling of temperature excursions once removed from the freezer

Stability data indicate that the unopened vial is stable for up to:

- 24 hours when stored at temperatures from -3 °C to 2 °C
- a total of 4 hours when stored at temperatures from 8 °C to 30 °C; this includes the 2 hours at up to 30 °C detailed above

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

Transfers of frozen vials stored at ultra-low temperature (< -60 °C)

- Closed-lid vial trays containing 195 vials removed from ultra-low temperature frozen storage (< -60 °C) may be at temperatures up to 25 °C for up to 5 minutes.
- Open-lid vial trays, or vial trays containing less than 195 vials, removed from ultra-low temperature frozen storage (< -60 °C) may be at temperatures up to 25 °C for up to 3 minutes.
- After vial trays are returned to frozen storage following temperature exposure up to 25 °C, they must remain in frozen storage for at least 2 hours before they can be removed again.

Transfers of frozen vials stored at -25 °C to -15 °C

- Closed-lid vial trays containing 195 vials removed from frozen storage (-25 °C to -15 °C) may be at temperatures up to 25 °C for up to 3 minutes.
- Open-lid vial trays, or vial trays containing less than 195 vials, removed from frozen storage (-25 °C to -15 °C) may be at temperatures up to 25 °C for up to 1 minute.

Once a vial is removed from the vial tray, it should be thawed for use.

Diluted medicinal product

Chemical and physical in-use stability, including during transportation, has been demonstrated for 6 hours at 2 °C to 30 °C after dilution in sodium chloride 9 mg/mL (0.9%) solution for injection. From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

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

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

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

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

6.5 Nature and contents of container

0.45 mL concentrate in a 2 mL clear multidose vial (type I glass) with a stopper (synthetic bromobutyl rubber) and a purple flip-off plastic cap with aluminium seal. Each vial contains 6 doses, see section 6.6.

Pack size: 195 vials

6.6 Special precautions for disposal and other handling

Handling instructions prior to use

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

- **Verify** that the vial has a **purple plastic cap** and the product **name is Comirnaty 30 micrograms/dose concentrate for dispersion for injection** (12 years and older).
- If the vial has another product name on the label, please make reference to the Summary of Product Characteristics for that formulation.
- The vial is stored frozen and must be thawed prior to dilution. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 195-vial pack may take 3 hours to thaw. Alternatively, frozen vials may also be thawed for 30 minutes at temperatures up to 30 °C for immediate use.

- The unopened vial can be **stored for up to 1 month at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP). Within the 1-month shelf life at 2 °C to 8 °C, up to 48 hours may be used for transportation.
- Allow the thawed vial to come to room temperature. Prior to use, the unopened vial can be stored for up to 2 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Dilution

- Gently invert the vial 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 **1.8 mL of 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 1.8 mL air into the empty diluent syringe.
- Gently invert the diluted dispersion 10 times. Do not shake.
- The diluted vaccine should present as an off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discolouration are present.
- The diluted vials should be marked with the appropriate **discard date and time**.
- **After dilution**, store at 2 °C to 30 °C and use within **6 hours**, including any transportation time.
- 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 2.25 mL from which 6 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.
Low dead-volume syringes and/or needles should be used in order to extract 6 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial.
- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
- Discard any unused vaccine within 6 hours after dilution.

Disposal

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

7. **MARKETING AUTHORISATION HOLDER**

BioNTech Manufacturing GmbH
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55131 Mainz
Germany
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Fax: +49 6131 9084-2121
service@biontech.de

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1528/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 December 2020

Date of latest renewal: 10 October 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

▼ 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 30 micrograms/dose dispersion for injection
COVID-19 mRNA Vaccine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

This is a single dose or a multidose vial with a grey cap. Do not dilute prior to use.

One single dose vial contains 1 dose of 0.3 mL, see sections 4.2 and 6.6.

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

One dose (0.3 mL) contains 30 micrograms of tozinameran, a COVID-19 mRNA Vaccine (nucleoside modified, embedded in lipid nanoparticles).

Tozinameran 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.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersion for injection.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Comirnaty 30 micrograms/dose dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 12 years of age and older.

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

4.2 Posology and method of administration

Posology

Individuals 12 years of age and older

Comirnaty 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 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Severely immunocompromised aged 12 years and older

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

Paediatric population

There are paediatric formulations available for infants aged 6 months and above and children below 12 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.

Elderly population

No dose adjustment is required in elderly individuals ≥ 65 years of age.

Method of administration

Comirnaty 30 micrograms/dose dispersion for injection should be administered intramuscularly (see section 6.6). Do not dilute prior to use.

The preferred site is the deltoid muscle of the upper arm.

Do not inject the vaccine intravascularly, subcutaneously or intradermally.

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

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

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

Single dose vials

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

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

Multidose vials

Multidose vials of Comirnaty 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, hypoesthesia and sweating) may occur in association with the vaccination process itself. Stress-related reactions are temporary and resolve on their own. Individuals should be advised to bring symptoms to the attention of the vaccination provider for evaluation. It is important that precautions are in place to avoid injury from fainting.

Concurrent illness

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

Thrombocytopenia and coagulation disorders

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

Immunocompromised individuals

The efficacy and safety of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of Comirnaty 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 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 with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

A large amount of observational data from pregnant women vaccinated with Comirnaty 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). Comirnaty can be used during pregnancy.

Breast-feeding

No effects on the breastfed newborn/infant are anticipated since the systemic exposure of breast-feeding woman to Comirnaty is negligible. Observational data from women who were breast-feeding after vaccination have not shown a risk for adverse effects in breastfed newborns/infants. Comirnaty 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 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

Participants 16 years of age and older – after 2 doses

In Study 2, a total of 22 026 participants 16 years of age or older received at least 1 dose of Comirnaty and a total of 22 021 participants 16 years of age or older received placebo (including 138 and 145 adolescents 16 and 17 years of age in the vaccine and placebo groups, respectively). A total of 20 519 participants 16 years of age or older received 2 doses of Comirnaty.

At the time of the analysis of Study 2 with a data cut-off of 13 March 2021 for the placebo-controlled blinded follow-up period up to the participants' unblinding dates, a total of 25 651 (58.2%) participants (13 031 Comirnaty and 12 620 placebo) 16 years of age and older were followed up for ≥ 4 months after the second dose. This included a total of 15 111 (7 704 Comirnaty and 7 407 placebo) participants 16 to 55 years of age and a total of 10 540 (5 327 Comirnaty and 5 213 placebo) participants 56 years of age and older.

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

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

Adolescents 12 to 15 years of age – after 2 doses

In an analysis of long-term safety follow-up in Study 2, 2 260 adolescents (1 131 Comirnaty and 1 129 placebo) were 12 to 15 years of age. Of these, 1 559 adolescents (786 Comirnaty and 773 placebo) have been followed for ≥ 4 months after the second dose of Comirnaty.

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

Participants 12 years of age and older – after booster dose

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 (see section 5.1).

Tabulated list of adverse reactions from clinical studies and post-authorisation experience in individuals 12 years of age and older

Adverse reactions observed during clinical studies are listed below according to the following frequency categories: Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1\ 000$ to $< 1/100$), Rare ($\geq 1/10\ 000$ to $< 1/1\ 000$), Very rare ($< 1/10\ 000$), Not known (cannot be estimated from the available data).

Table 1. Adverse reactions from Comirnaty clinical trials and post-authorisation experience in individuals 12 years of age and older

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
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 ^h
General disorders and administration site conditions	Very common	Injection site pain; fatigue; chills; pyrexia ^f ; injection site swelling
	Common	Injection site redness
	Uncommon	Asthenia; malaise; injection site pruritus
	Not known	Extensive swelling of vaccinated limb ^d ; facial swelling ^g

- In participants 5 years of age and older, a higher frequency of lymphadenopathy was reported after a booster ($\leq 2.8\%$) dose than after primary ($\leq 0.9\%$) doses of the vaccine.
- The frequency category for urticaria and angioedema was rare.
- Through the clinical trials safety follow-up period to 14 November 2020, acute peripheral facial paralysis (or palsy) was reported by four participants in the COVID-19 mRNA Vaccine group. Onset was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.
- Adverse reaction determined post-authorisation.
- Refers to vaccinated arm.
- A higher frequency of pyrexia was observed after the second dose compared to the first dose.
- Facial swelling in vaccine recipients with a history of injection of dermatological fillers has been reported in the post-marketing phase.
- Most cases appeared to be non-serious and temporary in nature.

Description of selected adverse reactions

Myocarditis and pericarditis

The increased risk of myocarditis after vaccination with Comirnaty is highest in younger males (see section 4.4).

Two large European pharmacoepidemiological studies have estimated the excess risk in younger males following the second dose of Comirnaty. One study showed that in a period of 7 days after the second dose there were about 0.265 (95% CI 0.255 - 0.275) extra cases of myocarditis in 12-29 year old males per 10 000 compared to unexposed persons. In another study, in a period of 28 days after the second dose there were 0.56 (95% CI 0.37 - 0.74) extra cases of myocarditis in 16-24 year old males per 10 000 compared to unexposed persons.

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#) and include batch/Lot number if available.

4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vaccines, viral vaccines, ATC code: J07BN01

Mechanism of action

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

Efficacy

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

significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrolment, were included as were participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis B virus (HBV).

Efficacy in participants 16 years of age and older – after 2 doses

In the Phase 2/3 portion of Study 2, based on data accrued through 14 November 2020, approximately 44 000 participants were randomised equally and were to receive 2 doses of COVID-19 mRNA Vaccine or placebo. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. The majority (93.1%) of vaccine recipients received the second dose 19 days to 23 days after Dose 1. Participants are planned to be followed for up to 24 months after Dose 2, for assessments of safety and efficacy against COVID-19. In the clinical study, participants were required to observe a minimum interval of 14 days before and after administration of an influenza vaccine in order to receive either placebo or COVID-19 mRNA Vaccine. In the clinical study, participants were required to observe a minimum interval of 60 days before or after receipt of blood/plasma products or immunoglobulins within through conclusion of the study in order to receive either placebo or COVID-19 mRNA Vaccine.

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

At the time of the primary efficacy analysis, participants had been followed for symptomatic COVID-19 for in total 2 214 person-years for the COVID-19 mRNA Vaccine and in total 2 222 person-years in the placebo group.

There were no meaningful clinical differences in overall vaccine efficacy in participants who were at risk of severe COVID-19 including those with 1 or more comorbidities that increase the risk of severe COVID-19 (e.g. asthma, body mass index (BMI) ≥ 30 kg/m², chronic pulmonary disease, diabetes mellitus, hypertension).

The vaccine efficacy information is presented in Table 2.

Table 2. 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 n^{1b} Surveillance time^c (n2^d)	Placebo N^a = 18 325 Cases n^{1b} 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 3.

Table 3. 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 4) 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 4. 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 $\leq 93\%$ on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen < 300 mm Hg);
- Respiratory failure [defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
- Evidence of shock (systolic blood pressure < 90 mm Hg, diastolic blood pressure < 60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an Intensive Care Unit;
- Death.

- a. n1 = Number of participants meeting the endpoint definition.
- b. n2 = Number of participants at risk for the endpoint.

- c. Two-side confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
- d. Efficacy assessed based on the Dose 1 all available efficacy (modified intention-to-treat) population that included all randomised participants who received at least 1 dose of study intervention.
- e. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.
- f. Efficacy assessed based on the evaluable efficacy (7 Days) population that included all eligible randomised participants who receive all dose(s) of study intervention as randomised within the predefined window, have no other important protocol deviations as determined by the clinician.
- g. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

Efficacy and immunogenicity in adolescents 12 to 15 years of age – after 2 doses

In an initial analysis of Study 2 in adolescents 12 to 15 years of age (representing a median follow-up duration of > 2 months after Dose 2) without evidence of prior infection, there were no cases in 1 005 participants who received the vaccine and 16 cases out of 978 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 75.3, 100.0). In participants with or without evidence of prior infection there were 0 cases in the 1 119 who received vaccine and 18 cases in 1 110 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 78.1, 100.0).

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

In the updated efficacy analysis of Study 2 in adolescents 12 to 15 years of age without evidence of prior infection, there were no cases in 1 057 participants who received the vaccine and 28 cases out of 1 030 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 86.8, 100.0) during the period when Alpha variant was the predominant circulating strain. In participants with or without evidence of prior infection there were 0 cases in the 1 119 who received vaccine and 30 cases in 1 109 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 87.5, 100.0).

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

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

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

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

Table 5. SARS-CoV-2 neutralization assay – NT50 (titre)[†] (SARS-CoV-2 USA_WA1/2020) – GMT and seroresponse rate comparison of 1 month after booster dose to 1 month after primary series – participants 18 through 55 years of age without evidence of infection up to 1 month after booster dose* – booster dose evaluable immunogenicity population[‡]

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

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

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

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

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

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

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

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

The relative vaccine efficacy information for participants 16 years of age and older without prior evidence of SARS-CoV-2 infection is presented in Table 6. 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 6. 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.

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

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

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

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

pseudovirus (wild-type), neutralising antibody NT50 GMR-fold change increased 21.6-fold with heterologous Comirnaty booster (n = 95).

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

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

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

In Substudy D [a subset from Study 2 (Phase 3) and Study 4 (Phase 3)], 325 participants 18 to ≤ 55 years of age who had completed 3 doses of Comirnaty received Comirnaty (30 mcg) as a booster dose (fourth dose) 90 to 180 days after receiving Dose 3. For the Immunogenicity subset data see Table 7.

Table 7. Summary of immunogenicity data from participants in C4591031 Substudy D (cohort 2 full expanded set) and Substudy E (expanded cohort immunogenicity subset) who received Comirnaty 30 mcg as booster (fourth dose) – participants without evidence of infection up to 1 month after booster dose – evaluable immunogenicity population

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

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

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

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

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

Note: Seroreponse is defined as achieving ≥ 4 -fold rise from baseline (before the study vaccination). If the baseline measurement is below the LLOQ, the post-vaccination measure of $\geq 4 \times \text{LLOQ}$ is considered a seroreponse.

- a. Protocol-specified timing for blood sample collection.
- b. N = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- c. N = Number of participants with valid and determinate assay results for the specified assay at both the pre-vaccination time point and the given sampling time point.
- d. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
- e. n = Number of participants with seroreponse for the given assay at the given sampling time point.
- f. Exact 2-sided CI, based on the Clopper and Pearson method.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Comirnaty in 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 neutralizing antibody responses were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in foetuses and offspring. There were no vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development. No Comirnaty data are available on vaccine placental transfer or excretion in milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened vial

Frozen vial

2 years when stored at -90 °C to -60 °C.

The vaccine will be received frozen at -90 °C to -60 °C. Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

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 or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Multidose vials

When stored frozen at -90 °C to -60 °C, 10-vial packs of multidose vials of the vaccine can be thawed at 2 °C to 8 °C for 6 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed vial

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

- Upon moving the vaccine to 2 °C to 8 °C storage, the updated expiry date must be written on the outer carton and the vaccine should be used or discarded by the updated expiry date. The original expiry date should be crossed out.
- If the vaccine is received at 2 °C to 8 °C it should be stored at 2 °C to 8 °C. The expiry date on the outer carton should have been updated to reflect the refrigerated expiry date and the original expiry date should have been crossed out.

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

Thawed vials can be handled in room light conditions.

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

Handling of temperature excursions during refrigerated storage

- Stability data indicate that the unopened vial is stable for up to 10 weeks when stored at temperatures from -2 °C to 2 °C, within the 10-week storage period between 2 °C and 8 °C.

- Stability data indicate the vial can be stored for up to 24 hours at temperatures of 8 °C to 30 °C, including up to 12 hours following first puncture.

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

Opened vial

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

6.4 Special precautions for storage

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

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

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

For storage conditions after thawing and first opening, see section 6.3.

6.5 Nature and contents of container

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

One single dose vial contains 1 dose of 0.3 mL, see sections 4.2 and 6.6.

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

Single dose vial pack size: 10 vials.

Multidose vial pack sizes: 10 vials or 195 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Handling instructions prior to use

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

- **Verify** that the vial has a **grey plastic cap** and the product **name is Comirnaty 30 micrograms/dose dispersion for injection** (12 years and older).
- If the vial has another product name on the label, please make reference to the Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw. Ensure vials are completely thawed prior to use.
 - 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).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Preparation of 0.3 mL doses

- Gently mix by inverting vials 10 times prior to use. Do not shake.
- Prior to mixing, the thawed dispersion may contain white to off-white opaque amorphous particles.
- After mixing, the vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the vaccine if particulates or discoloration 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.

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 vial. Discard any unused vaccine 12 hours after first puncture.

Disposal

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

Single dose vials

EU/1/20/1528/013

Multidose vials

EU/1/20/1528/002

EU/1/20/1528/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 December 2020

Date of latest renewal: 10 October 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

▼ 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 10 micrograms/dose concentrate for dispersion for injection
COVID-19 mRNA Vaccine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

One vial (1.3 mL) contains 10 doses of 0.2 mL after dilution, see sections 4.2 and 6.6.

One dose (0.2 mL) contains 10 micrograms of tozinameran, a COVID-19 mRNA Vaccine (nucleoside modified, embedded in lipid nanoparticles).

Tozinameran 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.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Comirnaty 10 micrograms/dose concentrate for dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in children aged 5 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 10 micrograms/dose 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 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Severely immunocompromised aged 5 years and older

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

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

Paediatric population

There are paediatric formulations available for infants and children aged 6 months to 4 years. For details, please refer to the 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 10 micrograms/dose concentrate for dispersion for injection should be administered intramuscularly after dilution (see section 6.6).

After dilution, vials of Comirnaty 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.

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, hypoesthesia and sweating) may occur in association with the vaccination process itself. Stress-related reactions are temporary and resolve on their own. Individuals should be advised to bring symptoms to the attention of the vaccination provider for evaluation. It is important that precautions are in place to avoid injury from fainting.

Concurrent illness

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

Thrombocytopenia and coagulation disorders

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

Immunocompromised individuals

The efficacy and safety of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of Comirnaty 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 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 with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

A large amount of observational data from pregnant women vaccinated with Comirnaty 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). Comirnaty can be used during pregnancy.

Breast-feeding

No effects on the breastfed newborn/infant are anticipated since the systemic exposure of breast-feeding woman to Comirnaty is negligible. Observational data from women who were breast-feeding after vaccination have not shown a risk for adverse effects in breastfed newborns/infants. Comirnaty 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 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

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 Comirnaty 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 ($\geq 20\%$), myalgia, chills, and diarrhoea ($> 10\%$).

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

In a subset from Study 3, a total of 401 children 5 to 11 years of age received a booster dose of Comirnaty 10 mcg at least 5 months (range of 5 to 9 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 22 March 2022 (median follow-up time of 1.3 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 were injection site pain ($> 70\%$), fatigue ($> 40\%$), headache ($> 30\%$), 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.

Tabulated list of adverse reactions from clinical studies and post-authorisation experience in individuals 5 years of age and older

Adverse reactions observed during clinical studies are listed below according to the following frequency categories: Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1\ 000$ to $< 1/100$), Rare ($\geq 1/10\ 000$ to $< 1/1\ 000$), Very rare ($< 1/10\ 000$), Not known (cannot be estimated from the available data).

Table 1. Adverse reactions from Comirnaty clinical trials and post-authorisation experience in individuals 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
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 ^f
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

- In participants 5 years of age and older, a higher frequency of lymphadenopathy was reported after a booster ($\leq 2.8\%$) dose than after primary ($\leq 0.9\%$) doses of the vaccine.
- The frequency category for urticaria and angioedema was rare.
- Through the clinical trials safety follow-up period to 14 November 2020, acute peripheral facial paralysis (or palsy) was reported by four participants in the COVID-19 mRNA Vaccine group. Onset was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.
- Adverse reaction determined post-authorisation.
- Refers to vaccinated arm.
- A higher frequency of pyrexia was observed after the second dose compared to the first dose.
- Facial swelling in vaccine recipients with a history of injection of dermatological fillers has been reported in the post-marketing phase.
- Injection site redness occurred at a higher frequency (very common) in children 5 to 11 years of age.
- Most cases appeared to be non-serious and temporary in nature.

Description of selected adverse reactions

Myocarditis and pericarditis

The increased risk of myocarditis after vaccination with Comirnaty is highest in younger males (see section 4.4).

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 listed in [Appendix V](#) and include batch/Lot number if available.

4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vaccines, viral vaccines, ATC code: J07BN01

Mechanism of action

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

Efficacy

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

significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrolment, were included as were participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis B virus (HBV).

Efficacy in participants 16 years of age and older – after 2 doses

In the Phase 2/3 portion of Study 2, based on data accrued through 14 November 2020, approximately 44 000 participants were randomised equally and were to receive 2 doses of COVID-19 mRNA Vaccine or placebo. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. The majority (93.1%) of vaccine recipients received the second dose 19 days to 23 days after Dose 1. Participants are planned to be followed for up to 24 months after Dose 2, for assessments of safety and efficacy against COVID-19. In the clinical study, participants were required to observe a minimum interval of 14 days before and after administration of an influenza vaccine in order to receive either placebo or COVID-19 mRNA Vaccine. In the clinical study, participants were required to observe a minimum interval of 60 days before or after receipt of blood/plasma products or immunoglobulins within through conclusion of the study in order to receive either placebo or COVID-19 mRNA Vaccine.

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

At the time of the primary efficacy analysis, participants had been followed for symptomatic COVID-19 for in total 2 214 person-years for the COVID-19 mRNA Vaccine and in total 2 222 person-years in the placebo group.

There were no meaningful clinical differences in overall vaccine efficacy in participants who were at risk of severe COVID-19 including those with 1 or more comorbidities that increase the risk of severe COVID-19 (e.g. asthma, body mass index (BMI) ≥ 30 kg/m², chronic pulmonary disease, diabetes mellitus, hypertension).

The vaccine efficacy information is presented in Table 2.

Table 2. 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 n^{1b} Surveillance time^c (n2^d)	Placebo N^a = 18 325 Cases n^{1b} 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.

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

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

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

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

The updated vaccine efficacy information is presented in Table 3.

Table 3. 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.

- N = Number of participants in the specified group.
- n1 = Number of participants meeting the endpoint definition.
- 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.
- n2 = Number of participants at risk for the endpoint.
- Two-sided 95% confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
- Included confirmed cases in participants 12 to 15 years of age: 0 in the COVID-19 mRNA Vaccine group; 16 in the placebo group.

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

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

Efficacy against severe COVID-19

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

As of 13 March 2021, vaccine efficacy against severe COVID-19 is presented only for participants with or without prior SARS-CoV-2 infection (Table 4) 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 4. 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 $\leq 93\%$ on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen < 300 mm Hg);
- Respiratory failure [defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
- Evidence of shock (systolic blood pressure < 90 mm Hg, diastolic blood pressure < 60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an Intensive Care Unit;
- Death.

- n1 = Number of participants meeting the endpoint definition.

- b. n_2 = 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 5. 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 5. 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.

- N = Number of participants in the specified group.
- n1 = Number of participants meeting the endpoint definition.
- 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.
- 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 prespecified immunobridging criteria for both the geometric mean ratio (GMR) and the seroresponse difference with seroresponse defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from baseline (before Dose 1).

The GMR of the SARS-CoV-2 NT50 1 month after Dose 2 in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) to that of young adults 16 to 25 years of age was 1.04 (2-sided 95% CI: 0.93, 1.18). Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, 99.2% of children 5 to 11 years of age and 99.2% of participants 16 to 25 years of age had a seroresponse at 1 month after Dose 2. The difference in proportions of participants who had seroresponse between the 2 age groups (children – young adult) was 0.0% (2-sided 95% CI: -2.0%, 2.2%). This information is presented in Table 6.

Table 6. Summary of geometric mean ratio for 50% neutralising titre and difference in percentages of participants with seroresponse – comparison of children 5 to 11 years of age (Study 3) to participants 16 to 25 years of age (Study 2) – participants without evidence of infection up to 1 month after Dose 2 – immunobridging subset – Phase 2/3 – evaluable immunogenicity population

		COVID-19 mRNA Vaccine		5 to 11 years/ 16 to 25 years	
		10 mcg/dose 5 to 11 years N ^a =264	30 mcg/dose 16 to 25 years N ^a =253		
	Time point ^b	GMT ^c (95% CI ^e)	GMT ^c (95% CI ^e)	GMR ^d (95% CI ^d)	Met immunobridging objective ^e (Y/N)
Geometric mean 50% neutralizing 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% neutralizing 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 postvaccination assay result $\geq 4 \times$ LLOQ is considered a seroresponse.

- N = Number of participants with valid and determinate assay results before vaccination and at 1 month after Dose 2. These values are also the denominators used in the percentage calculations for seroresponse rates.
- Protocol-specified timing for blood sample collection.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (5 to 11 years of age minus 16 to 25 years of age) and the corresponding CI (based on the Student t distribution).
- Immunobridging based on GMT is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥ 0.8 .
- SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralisation is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralised.
- n = Number of participants with seroresponse based on NT50 1 month after Dose 2.
- Exact 2-sided CI based on the Clopper and Pearson method.
- Difference in proportions, expressed as a percentage (5 to 11 years of age minus 16 to 25 years of age).
- 2-Sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
- Immunobridging based on seroresponse rate is declared if the lower bound of the 2-sided 95% CI for the seroresponse difference is greater than -10.0%.

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

A booster dose of Comirnaty was given to 401 randomly selected participants in Study 3. Effectiveness of a booster dose in ages 5 to 11 is inferred by immunogenicity. The immunogenicity of this was assessed through NT50 against the reference strain of SARS-CoV-2 (USA_WA1/2020). Analyses of NT50 1 month after the booster dose compared to before the booster dose demonstrated a substantial increase in GMTs in individuals 5 through 11 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the dose 2 and the booster dose. This analysis is summarized in Table 7.

Table 7. Summary of geometric mean titres – NT50 – participants without evidence of infection – phase 2/3 – immunogenicity set – 5 through 11 years of age – evaluable immunogenicity population

Assay	Sampling time point ^a		1 month after booster dose/ 1 month after dose 2
	1 month after booster dose (n ^b =67)	1 month after dose 2 (n ^b =96)	
	GMT ^c (95% CI ^c)	GMT ^c (95% CI ^c)	GMR ^d (95% CI ^d)
SARS-CoV-2 neutralization 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% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

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

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Comirnaty in 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 neutralizing antibody responses were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in foetuses and offspring. There were no vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development. No Comirnaty data are available on vaccine placental transfer or excretion in milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

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

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

Cholesterol

Trometamol

Trometamol hydrochloride

Sucrose

Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial

Frozen vial

2 years when stored at -90 °C to -60 °C.

The vaccine will be received frozen at -90 °C to -60 °C. Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

When stored frozen at -90 °C to -60 °C, 10-vial packs of the vaccine can be thawed at 2 °C to 8 °C for 4 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed vial

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

- Upon moving the vaccine to 2 °C to 8 °C storage, the updated expiry date must be written on the outer carton and the vaccine should be used or discarded by the updated expiry date. The original expiry date should be crossed out.

- If the vaccine is received at 2 °C to 8 °C it should be stored at 2 °C to 8 °C. The expiry date on the outer carton should have been updated to reflect the refrigerated expiry date and the original expiry date should have been crossed out.

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

Thawed vials can be handled in room light conditions.

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

Handling of temperature excursions during refrigerated storage

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

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

Diluted medicinal product

Chemical and physical in-use stability has been demonstrated for 12 hours at 2 °C to 30 °C, after dilution with sodium chloride 9 mg/mL (0.9%) solution for injection, which includes up to 6 hours transportation time. From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

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

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

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

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

6.5 Nature and contents of container

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 sizes: 10 vials or 195 vials

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Handling instructions prior to use

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

- **Verify that the vial has an orange plastic cap and the product name is Comirnaty 10 micrograms/dose concentrate for dispersion for injection (children 5 to 11 years).**
- If the vial has another product name on the label, please make reference to the Summary of Product Characteristics 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 4 hours to thaw. Ensure vials are completely thawed prior to use.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Dilution

- 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 **1.3 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 1.3 mL air into the empty diluent syringe.
- Gently invert the diluted dispersion 10 times. Do not shake.
- The diluted vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discolouration are present.
- The diluted vials should be marked with the appropriate **discard date and time**.
- **After dilution**, store at 2 °C to 30 °C and use within **12 hours**.
- Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.

Preparation of 0.2 mL doses

- 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 for children aged 5 to 11 years.
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 12 hours after dilution.

Disposal

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

7. MARKETING AUTHORISATION HOLDER

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55131 Mainz
Germany
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Fax: +49 6131 9084-2121
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8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1528/004
EU/1/20/1528/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 December 2020
Date of latest renewal: 10 October 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

▼ 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 3 micrograms/dose concentrate for dispersion for injection
COVID-19 mRNA Vaccine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

One vial (0.4 mL) contains 10 doses of 0.2 mL after dilution, see sections 4.2 and 6.6.

One dose (0.2 mL) contains 3 micrograms of tozinameran, a COVID-19 mRNA Vaccine (nucleoside modified, embedded in lipid nanoparticles).

Tozinameran 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.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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 3 micrograms/dose is administered intramuscularly after dilution as a primary course of 3 doses (0.2 mL each). It is recommended to administer the second dose 3 weeks after the first dose followed by a third dose administered at least 8 weeks after the second dose (see sections 4.4 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 3 micrograms/dose is administered intramuscularly after dilution as a single dose of 0.2 mL for infants and children 6 months to 4 years of age.

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

Severely immunocompromised aged 6 months to 4 years

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

Interchangeability

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

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

Paediatric population

There are paediatric formulations available for children 5 to 11 years of age. For details, please refer to the 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 3 micrograms/dose concentrate for dispersion for injection should be administered intramuscularly after dilution (see section 6.6).

After dilution, vials of Comirnaty 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.

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, hypoesthesia and sweating) may occur in association with the vaccination process itself. Stress-related reactions are temporary and resolve on their own. Individuals should be advised to bring symptoms to the attention of the vaccination provider for evaluation. It is important that precautions are in place to avoid injury from fainting.

Concurrent illness

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

Thrombocytopenia and coagulation disorders

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

Immunocompromised individuals

The efficacy and safety of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of Comirnaty 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 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 with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation

Comirnaty 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 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

Infants 6 to 23 months of age – after 3 doses

In an analysis of Study 3 (Phase 2/3), 1 776 infants (1 178 Comirnaty 3 mcg and 598 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 29 April 2022, 570 infants 6 to 23 months of age who received a 3-dose primary course (386 Comirnaty 3 mcg and 184 placebo) have been followed for a median of 1.3 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), 2 750 children (1 835 Comirnaty 3 mcg and 915 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 29 April 2022, 886 children 2 to 4 years of age who received a 3-dose primary course (606 Comirnaty 3 mcg and 280 placebo) have been followed a median of 1.4 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 Comirnaty 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 ($\geq 20\%$), myalgia, chills, and diarrhoea ($> 10\%$).

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

In a subset from Study 3, a total of 401 children 5 to 11 years of age received a booster dose of Comirnaty 10 mcg at least 5 months (range of 5 to 9 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 22 March 2022 (median follow-up time of 1.3 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 were injection site pain ($> 70\%$), fatigue ($> 40\%$), headache ($> 30\%$), 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 \geq 4 months after the booster dose of Comirnaty. No new adverse reactions of Comirnaty were identified.

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

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

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

Tabulated list of adverse reactions from clinical studies and post-authorisation experience in individuals 6 months of age and older

Adverse reactions observed during clinical studies are listed below according to the following frequency categories: Very common (\geq 1/10), Common (\geq 1/100 to < 1/10), Uncommon (\geq 1/1 000 to < 1/100), Rare (\geq 1/10 000 to < 1/1 000), Very rare (< 1/10 000), Not known (cannot be estimated from the available data).

Table 1. Adverse reactions from Comirnaty clinical trials and post-authorisation experience in individuals 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
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

System Organ Class	Frequency	Adverse reactions
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

- In participants 5 years of age and older, a higher frequency of lymphadenopathy was reported after a booster ($\leq 2.8\%$) dose than after primary ($\leq 0.9\%$) doses of the vaccine.
- The frequency category for angioedema was rare.
- Through the clinical trial safety follow-up period to 14 November 2020, acute peripheral facial paralysis (or palsy) was reported by four participants in the COVID-19 mRNA Vaccine group. Onset was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.
- Adverse reaction determined post-authorization.
- Refers to vaccinated arm.
- A higher frequency of pyrexia was observed after the second dose compared to the first dose.
- Facial swelling in vaccine recipients with a history of injection of dermatological fillers has been reported in the post-marketing phase.
- Injection site redness occurred at a higher frequency (very common) in participants 6 months to 11 years of age.
- The frequency category for rash was common in participants 6 to 23 months of age.
- The frequency category for decreased appetite was very common in participants 6 to 23 months of age.
- Irritability, injection site tenderness, and drowsiness pertain to participants 6 to 23 months of age.
- Most cases appeared to be non-serious and temporary in nature.

Description of selected adverse reactions

Myocarditis and pericarditis

The increased risk of myocarditis after vaccination with Comirnaty is highest in younger males (see section 4.4).

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 listed in [Appendix V](#) and include batch/Lot number if available.

4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vaccines, viral vaccines, ATC code: J07BN01

Mechanism of action

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

Efficacy

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

Efficacy in participants 16 years of age and older – after 2 doses

In the Phase 2/3 portion of Study 2, based on data accrued through 14 November 2020, approximately 44 000 participants were randomised equally and were to receive 2 doses of COVID-19 mRNA Vaccine or placebo. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. The majority (93.1%) of vaccine recipients received the second dose 19 days to 23 days after Dose 1. Participants are planned to be followed for up to 24 months after Dose 2, for assessments of safety and efficacy against COVID-19. In the clinical study, participants were required to observe a minimum interval of 14 days before and after administration of an influenza vaccine in order to receive either placebo or COVID-19 mRNA Vaccine. In the clinical study, participants were required to observe a minimum interval of 60 days before or after receipt of blood/plasma products or immunoglobulins within through conclusion of the study in order to receive either placebo or COVID-19 mRNA Vaccine.

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

At the time of the primary efficacy analysis, participants had been followed for symptomatic COVID-19 for in total 2 214 person-years for the COVID-19 mRNA Vaccine and in total 2 222 person-years in the placebo group.

There were no meaningful clinical differences in overall vaccine efficacy in participants who were at risk of severe COVID-19 including those with 1 or more comorbidities that increase the risk of severe COVID-19 (e.g. asthma, body mass index (BMI) ≥ 30 kg/m², chronic pulmonary disease, diabetes mellitus, hypertension).

The vaccine efficacy information is presented in Table 2.

Table 2. 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.

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

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

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

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

The updated vaccine efficacy information is presented in Table 3.

Table 3. 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.

- N = Number of participants in the specified group.
- n1 = Number of participants meeting the endpoint definition.
- 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.
- n2 = Number of participants at risk for the endpoint.
- Two-sided 95% confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
- Included confirmed cases in participants 12 to 15 years of age: 0 in the COVID-19 mRNA Vaccine group; 16 in the placebo group.

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

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

Efficacy against severe COVID-19

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

As of 13 March 2021, vaccine efficacy against severe COVID-19 is presented only for participants with or without prior SARS-CoV-2 infection (Table 4) 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 4. 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 $\leq 93\%$ on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen < 300 mm Hg);
- Respiratory failure [defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
- Evidence of shock (systolic blood pressure < 90 mm Hg, diastolic blood pressure < 60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an Intensive Care Unit;
- Death.

- a. n1 = Number of participants meeting the endpoint definition.
- b. n2 = Number of participants at risk for the endpoint.
- c. Two-side confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
- d. Efficacy assessed based on the Dose 1 all available efficacy (modified intention-to-treat) population that included all randomised participants who received at least 1 dose of study intervention.
- e. Total surveillance time in 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 5. 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 5. 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 prespecified immunobridging criteria for both the geometric mean ratio (GMR) and the seroresponse difference with seroresponse defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from baseline (before Dose 1).

The GMR of the SARS-CoV-2 NT50 1 month after Dose 2 in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) to that of young adults 16 to 25 years of age was 1.04 (2-sided 95% CI: 0.93, 1.18). Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, 99.2% of children 5 to 11 years of age and 99.2% of participants 16 to 25 years of age had a seroresponse at 1 month after Dose 2. The difference in proportions of participants who had seroresponse between the 2 age groups (children – young adult) was 0.0% (2-sided 95% CI: -2.0%, 2.2%). This information is presented in Table 6.

Table 6. Summary of geometric mean ratio for 50% neutralising titre and difference in percentages of participants with seroresponse – comparison of children 5 to 11 years of age (Study 3) to participants 16 to 25 years of age (Study 2) – participants without evidence of infection up to 1 month after Dose 2 – immunobridging subset – Phase 2/3 – evaluable immunogenicity population

		COVID-19 mRNA Vaccine		5 to 11 years/ 16 to 25 years	
		10 mcg/dose 5 to 11 years N ^a =264	30 mcg/dose 16 to 25 years N ^a =253		
	Time point ^b	GMT ^c (95% CI ^e)	GMT ^c (95% CI ^e)	GMR ^d (95% CI ^e)	Met immunobridging objective ^e (Y/N)
Geometric mean 50% neutralizing 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% neutralizing 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 postvaccination assay result $\geq 4 \times$ LLOQ is considered a seroresponse.

- N = Number of participants with valid and determinate assay results before vaccination and at 1 month after Dose 2. These values are also the denominators used in the percentage calculations for seroresponse rates.
- Protocol-specified timing for blood sample collection.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (5 to 11 years of age minus 16 to 25 years of age) and the corresponding CI (based on the Student t distribution).
- Immunobridging based on GMT is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥ 0.8 .
- SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralisation is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralised.
- n = Number of participants with seroresponse based on NT50 1 month after Dose 2.
- Exact 2-sided CI based on the Clopper and Pearson method.
- Difference in proportions, expressed as a percentage (5 to 11 years of age minus 16 to 25 years of age).
- 2-Sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
- Immunobridging based on seroresponse rate is declared if the lower bound of the 2-sided 95% CI for the seroresponse difference is greater than -10.0%.

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

A booster dose of Comirnaty was given to 401 randomly selected participants in Study 3. Effectiveness of a booster dose in ages 5 to 11 is inferred by immunogenicity. The immunogenicity of this was assessed through NT50 against the reference strain of SARS-CoV-2 (USA_WA1/2020). Analyses of NT50 1 month after the booster dose compared to before the booster dose demonstrated a substantial increase in GMTs in individuals 5 through 11 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the dose 2 and the booster dose. This analysis is summarized in Table 7.

Table 7. Summary of geometric mean titres – NT50 – participants without evidence of infection – phase 2/3 – immunogenicity set – 5 through 11 years of age – evaluable immunogenicity population

Assay	Sampling time point ^a		1 month after booster dose/ 1 month after dose 2 GMR ^d (95% CI ^d)
	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)	
SARS-CoV-2 neutralization 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% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ 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 through 4 years of age based on cases confirmed among 873 participants in the COVID-19 mRNA Vaccine group and 381 participants in the placebo group (2:1 randomization ratio) who received all 3 doses of study intervention during the blinded follow-up period when the Omicron variant of SARS-CoV-2 (BA.2) was the predominant variant in circulation (data cut-off date of 17 June 2022).

The vaccine efficacy results after Dose 3 in participants 6 months through 4 years of age are presented in Table 8.

Table 8. 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 through 4 years ^e	13 0.124 (794)	21 0.054 (351)	73.2 (43.8, 87.6)
2 through 4 years	9 0.081 (498)	13 0.033 (204)	71.8 (28.6, 89.4)
6 months through 23 months	4 0.042 (296)	8 0.020 (147)	75.8 (9.7, 94.7)

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

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

- N = number of participants in the specified group.
- n1 = Number of participants meeting the endpoint definition.
- 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.
- n2 = Number of participants at risk for the endpoint.
- Two-sided 95% confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.

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

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

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

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

The primary immunobridging analyses compared the geometric mean titres (using a geometric mean ratio [GMR]) and the seroresponse (defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from before Dose 1) rates in the evaluable immunogenicity population of participants without evidence of prior SARS-CoV-2 infection up to 1 month after Dose 3 in participants 6 to 23 months of age and 2 to 4 years of age and up to 1 month after Dose 2 in participants 16 to 25 years of age. The prespecified immunobridging criteria were met for both the GMR and the seroresponse difference for both age groups (Table 9).

Table 9. 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 neutralization 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 neutralization 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) ^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: Seroreponse is defined as achieving a ≥ 4 -fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result $\geq 4 \times$ LLOQ is considered a seroreponse.

- 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 seroreponse 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 $0.5 \times$ 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 neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralised.
- f. n = Number of participants with seroreponse 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 seroreponse 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.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Comirnaty in 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 neutralizing antibody responses were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in foetuses and offspring. There were no vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development. No Comirnaty data are available on vaccine placental transfer or excretion in milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial

Frozen vial

2 years when stored at -90 °C to -60 °C.

The vaccine will be received frozen at -90 °C to -60 °C. Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

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

Thawed vial

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

- Upon moving the vaccine to 2 °C to 8 °C storage, the updated expiry date must be written on the outer carton and the vaccine should be used or discarded by the updated expiry date. The original expiry date should be crossed out.
- If the vaccine is received at 2 °C to 8 °C it should be stored at 2 °C to 8 °C. The expiry date on the outer carton should have been updated to reflect the refrigerated expiry date and the original expiry date should have been crossed out.

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

Thawed vials can be handled in room light conditions.

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

Handling of temperature excursions during refrigerated storage

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

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

Diluted medicinal product

Chemical and physical in-use stability has been demonstrated for 12 hours at 2 °C to 30 °C, after dilution with sodium chloride 9 mg/mL (0.9%) solution for injection, which includes up to 6 hours transportation time. From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

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

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

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

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

6.5 Nature and contents of container

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

6.6 Special precautions for disposal and other handling

Handling instructions prior to use

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

- **Verify** that the vial has a **maroon plastic cap** and the product **name is Comirnaty 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, please make reference to the Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 10-vial pack may take 2 hours to thaw. Ensure vials are completely thawed prior to use.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.

- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Dilution

- 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 **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 2.2 mL air into the empty diluent syringe.
- Gently invert the diluted dispersion 10 times. Do not shake.
- The diluted vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discolouration are present.
- The diluted vials should be marked with the appropriate **discard date and time**.
- **After dilution**, store at 2 °C to 30 °C and use within **12 hours**.
- Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.

Preparation of 0.2 mL doses

- 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 for infants and children aged 6 months to 4 years.
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 12 hours after dilution.

Disposal

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

7. MARKETING AUTHORISATION HOLDER

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 Germany
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8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1528/010

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 December 2020

Date of latest renewal: 10 October 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

▼ 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 Original/Omicron BA.1 (15/15 micrograms)/dose dispersion for injection
COVID-19 mRNA Vaccine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

This is a multidose vial with a grey cap. Do not dilute prior to use.

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

One dose (0.3 mL) contains 15 micrograms of tozinameran and 15 micrograms of riltazinameran, a COVID-19 mRNA Vaccine (nucleoside modified, embedded in lipid nanoparticles).

Tozinameran 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 (Original). Riltazinameran 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 BA.1).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersion for injection.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Comirnaty Original/Omicron BA.1 (15/15 micrograms)/dose dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 12 years of age and older who have previously received at least a primary vaccination course against COVID-19 (see sections 4.2 and 5.1).

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 Original/Omicron BA.1 is administered intramuscularly as a single dose of 0.3 mL for individuals 12 years of age and older who have previously received at least a primary vaccination course against COVID-19 (see sections 4.4 and 5.1).

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

Severely immunocompromised aged 12 years and older

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

Paediatric population

There are paediatric formulations available for infants aged 6 months and above and children below 12 years of age. For details, please refer to the Summary of Product Characteristics for other formulations.

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

Elderly population

No dose adjustment is required in elderly individuals ≥ 65 years of age.

Method of administration

Comirnaty Original/Omicron BA.1 (15/15 micrograms)/dose dispersion for injection should be administered intramuscularly (see section 6.6). Do not dilute prior to use.

Vials of Comirnaty Original/Omicron BA.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.

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

The efficacy and safety of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of Comirnaty Original/Omicron BA.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 Original/Omicron BA.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 Original/Omicron BA.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 Original/Omicron BA.1 during pregnancy.

However, a large amount of observational data from pregnant women vaccinated with the initially approved Comirnaty vaccine during the second and third trimester have not shown an increase in adverse pregnancy outcomes. While data on pregnancy outcomes following vaccination during the first trimester are presently limited, no increased risk for miscarriage has been seen. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development (see section 5.3). Since differences between products are confined to the spike protein sequence, and there are no clinically meaningful differences in reactogenicity, Comirnaty Original/Omicron BA.1 can be used during pregnancy.

Breast-feeding

No data are available yet regarding the use of Comirnaty Original/Omicron BA.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 Original/Omicron BA.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 Original/Omicron BA.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

Comirnaty Original/Omicron BA.1

Participants > 55 years of age – after a booster dose of Comirnaty Original/Omicron BA.1 (fourth dose)

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 Original/Omicron BA.1 (15/15 mcg) 4.7 to 11.5 months after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty Original/Omicron BA.1 had a median follow-up time of at least 1.7 months.

The overall safety profile for the Comirnaty Original/Omicron BA.1 booster (fourth dose) was similar to that seen after the Comirnaty booster (third dose). The most frequent adverse reactions in participants greater than 55 years of age were injection site pain (> 50%), fatigue (> 40%), headache (> 30%), myalgia (> 20%), chills and arthralgia (> 10%). No new adverse reactions were identified for Comirnaty Original/Omicron BA.1.

Participants 18 to ≤ 55 years of age – after a booster dose of monovalent Omicron BA.1 (fourth dose)
The safety of a Comirnaty Original/Omicron BA.1 booster dose in individuals from 18 to ≤ 55 years of age is extrapolated from safety data from a subset of 315 adults 18 to ≤ 55 years of age who received a booster (fourth dose) of Omicron BA.1 30 mcg (monovalent) after completing 3 doses of Comirnaty. The most frequent adverse reactions in these participants 18 to ≤ 55 years of age were injection site pain (> 70%), fatigue (> 60%), headache (> 40%), myalgia (> 30%), chills (> 30%) and arthralgia (> 20%).

Comirnaty 30 mcg

Participants 16 years of age and older – after 2 doses

In Study 2, a total of 22 026 participants 16 years of age or older received at least 1 dose of Comirnaty and a total of 22 021 participants 16 years of age or older received placebo (including 138 and 145 adolescents 16 and 17 years of age in the vaccine and placebo groups, respectively). A total of 20 519 participants 16 years of age or older received 2 doses of Comirnaty.

At the time of the analysis of Study 2 with a data cut-off of 13 March 2021 for the placebo-controlled blinded follow-up period up to the participants' unblinding dates, a total of 25 651 (58.2%) participants (13 031 Comirnaty and 12 620 placebo) 16 years of age and older were followed up for ≥ 4 months after the second dose. This included a total of 15 111 (7 704 Comirnaty and 7 407 placebo) participants 16 to 55 years of age and a total of 10 540 (5 327 Comirnaty and 5 213 placebo) participants 56 years of age and older.

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

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

Adolescents 12 to 15 years of age – after 2 doses

In an analysis of long-term safety follow-up in Study 2, 2 260 adolescents (1 131 Comirnaty and 1 129 placebo) were 12 to 15 years of age. Of these, 1 559 adolescents (786 Comirnaty and 773 placebo) have been followed for ≥ 4 months after the second dose of Comirnaty.

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

Participants 12 years of age and older – after booster dose

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 (see section 5.1).

Tabulated list of adverse reactions from clinical studies of Comirnaty and Comirnaty Original/Omicron BA.1 and post-authorisation experience of Comirnaty in individuals 12 years of age and older

Adverse reactions observed during clinical studies are listed below according to the following frequency categories: Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1\ 000$ to $< 1/100$), Rare ($\geq 1/10\ 000$ to $< 1/1\ 000$), Very rare ($< 1/10\ 000$), Not known (cannot be estimated from the available data).

Table 1. Adverse reactions from Comirnaty and Comirnaty Original/Omicron BA.1 clinical trials and Comirnaty post-authorisation experience in individuals 12 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
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 ^h

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
	Uncommon	Asthenia; malaise; injection site pruritus
	Not known	Extensive swelling of vaccinated limb ^d ; facial swelling ^g

- In participants 5 years of age and older, a higher frequency of lymphadenopathy was reported after a booster ($\leq 2.8\%$) dose than after primary ($\leq 0.9\%$) doses of the vaccine.
- The frequency category for urticaria and angioedema was rare.
- Through the clinical trial safety follow-up period to 14 November 2020, acute peripheral facial paralysis (or palsy) was reported by four participants in the COVID-19 mRNA Vaccine group. Onset was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.
- Adverse reaction determined post-authorization.
- Refers to vaccinated arm.
- A higher frequency of pyrexia was observed after the second dose compared to the first dose.
- Facial swelling in vaccine recipients with a history of injection of dermatological fillers has been reported in the post-marketing phase.
- Most cases appeared to be non-serious and temporary in nature.

Description of selected adverse reactions

Myocarditis and pericarditis

The increased risk of myocarditis after vaccination with Comirnaty is highest in younger males (see section 4.4).

Two large European pharmacoepidemiological studies have estimated the excess risk in younger males following the second dose of Comirnaty. One study showed that in a period of 7 days after the second dose there were about 0.265 (95% CI 0.255 - 0.275) extra cases of myocarditis in 12-29 year old males per 10 000 compared to unexposed persons. In another study, in a period of 28 days after the second dose there were 0.56 (95% CI 0.37 - 0.74) extra cases of myocarditis in 16-24 year old males per 10 000 compared to unexposed persons.

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#) and include batch/Lot number if available.

4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vaccines, viral vaccines, ATC code: J07BN01

Mechanism of action

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

Efficacy

Comirnaty Original/Omicron BA.1

Relative vaccine immunogenicity in participants > 55 years of age – after a booster dose of Comirnaty Original/Omicron BA.1 (fourth dose)

In an interim analysis of a subset from Study 4 (Substudy E), 610 adults greater than 55 years of age who had completed a series of 3 doses of Comirnaty received 1 of the following as a booster dose (fourth dose): Comirnaty (30 mcg) or Comirnaty Original/Omicron BA.1 (15/15 mcg). GMRs and seroresponse rates were evaluated at 1 month after Comirnaty Original/Omicron BA.1 (15/15 mcg) booster vaccination up to a data cut-off date of 16 May 2022, which represents a median of at least 1.7 months post-booster follow-up. The Comirnaty Original/Omicron BA.1 (15/15 mcg) booster dose was administered 4.7 to 11.5 months (median 6.3 months) after the third dose.

The primary objective of the analysis was to assess superiority with respect to level of neutralising titre and noninferiority with respect to seroresponse rate of the anti-Omicron immune response induced by a dose of Comirnaty Original/Omicron BA.1 (15/15 mcg) relative to the response elicited by a dose of Comirnaty (30 mcg) given as a fourth dose in Comirnaty-experienced participants greater than 55 years of age.

Superiority of Comirnaty Original/Omicron BA.1 (15/15 mcg) to Comirnaty (30 mcg) was met, as the lower bound of the 2-sided 95% CI for GMR was > 1 (Table 2).

Seroresponse is defined as achieving ≥ 4 -fold rise from baseline (before the study vaccination). If the baseline measurement is below the LLOQ, the postvaccination measure of $\geq 4 \times$ LLOQ is considered a seroresponse.

The difference in percentages of participants who achieved seroresponse to Omicron variant between the Comirnaty Original/Omicron BA.1 group (71.6%) and Comirnaty group (57%) was 14.6% (2-sided 95% CI: 4.0%, 24.9%). Thus, noninferiority was met.

Table 2. Substudy E - Geometric mean ratios for between vaccine group comparison – participants without evidence of infection up to 1 month after Dose 4 – expanded cohort – immunogenicity subset – participants greater than 55 years of age – evaluable immunogenicity population

Assay	Vaccine group (as randomised)	Sampling time point ^a	N ^b	GMT (95% CI) ^c	GMR (95% CI) ^d
SARS-CoV-2 neutralisation assay -	Comirnaty (30 mcg)	1 month	163	455.8 (365.9, 567.6)	

Assay	Vaccine group (as randomised)	Sampling time point ^a	N ^b	GMT (95% CI) ^c	GMR (95% CI) ^d
Omicron BA.1 - NT50 (titre)	Comirnaty Original/Omicron BA.1 (15/15 mcg)	1 month	178	711.0 (588.3, 859.2)	1.56 (1.17, 2.08)
SARS-CoV-2 neutralisation assay - reference strain - NT50 (titre)	Comirnaty (30 mcg)	1 month	182	5 998.1 (5 223.6, 6 887.4)	
	Comirnaty Original/Omicron BA.1 (15/15 mcg)	1 month	186	5 933.2 (5 188.2, 6 785.2)	0.99 (0.82, 1.20)

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

Note: Immunogenicity subset = a random sample of 230 participants in each vaccine group selected from the expanded cohort.

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

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (vaccine group in the corresponding row - Comirnaty [30 mcg]) and the corresponding CI (based on the Student t distribution).

Comirnaty 30 mcg

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

Efficacy in participants 16 years of age and older – after 2 doses

In the Phase 2/3 portion of Study 2, based on data accrued through 14 November 2020, approximately 44 000 participants were randomised equally and were to receive 2 doses of COVID-19 mRNA Vaccine or placebo. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. The majority (93.1%) of vaccine recipients received the second dose 19 days to 23 days after Dose 1. Participants are planned to be followed for up to 24 months after Dose 2, for assessments of safety and efficacy against COVID-19. In the clinical study, participants were required to observe a minimum interval of 14 days before and after administration of an influenza vaccine in order to receive either placebo or COVID-19 mRNA Vaccine. In the clinical study, participants were required to observe a minimum interval of 60 days before or after receipt of blood/plasma products or immunoglobulins within through conclusion of the study in order to receive either placebo or COVID-19 mRNA Vaccine.

The population for the analysis of the primary efficacy endpoint included 36 621 participants 12 years of age and older (18 242 in the COVID-19 mRNA Vaccine group and 18 379 in the placebo group)

who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose. In addition, 134 participants were between the ages of 16 to 17 years of age (66 in the COVID-19 mRNA Vaccine group and 68 in the placebo group) and 1 616 participants 75 years of age and older (804 in the COVID-19 mRNA Vaccine group and 812 in the placebo group).

At the time of the primary efficacy analysis, participants had been followed for symptomatic COVID-19 for in total 2 214 person-years for the COVID-19 mRNA Vaccine and in total 2 222 person-years in the placebo group.

There were no meaningful clinical differences in overall vaccine efficacy in participants who were at risk of severe COVID-19 including those with 1 or more comorbidities that increase the risk of severe COVID-19 (e.g. asthma, body mass index (BMI) ≥ 30 kg/m², chronic pulmonary disease, diabetes mellitus, hypertension).

The vaccine efficacy information is presented in Table 3.

Table 3. 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 n^{1b} Surveillance time^c (n^{2d})	Placebo N^a = 18 325 Cases n^{1b} Surveillance time^c (n^{2d})	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.

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

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

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

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

The updated vaccine efficacy information is presented in Table 4.

Table 4. 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.

- N = Number of participants in the specified group.
- n1 = Number of participants meeting the endpoint definition.
- 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.
- n2 = Number of participants at risk for the endpoint.
- Two-sided 95% confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
- Included confirmed cases in participants 12 to 15 years of age: 0 in the COVID-19 mRNA Vaccine group; 16 in the placebo group.

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

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

Efficacy against severe COVID-19

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

As of 13 March 2021, vaccine efficacy against severe COVID-19 is presented only for participants with or without prior SARS-CoV-2 infection (Table 5) 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 5. 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 $\leq 93\%$ on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen < 300 mm Hg);
- Respiratory failure [defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
- Evidence of shock (systolic blood pressure < 90 mm Hg, diastolic blood pressure < 60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an Intensive Care Unit;
- Death.

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

b. n2 = Number of participants at risk for the endpoint.

c. Two-side confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.

d. Efficacy assessed based on the Dose 1 all available efficacy (modified intention-to-treat) population that included all randomised participants who received at least 1 dose of study intervention.

e. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.

f. Efficacy assessed based on the evaluable efficacy (7 Days) population that included all eligible randomised participants who receive all dose(s) of study intervention as randomised within the predefined window, have no other important protocol deviations as determined by the clinician.

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

Efficacy and immunogenicity in adolescents 12 to 15 years of age – after 2 doses

In an initial analysis of Study 2 in adolescents 12 to 15 years of age (representing a median follow-up duration of > 2 months after Dose 2) without evidence of prior infection, there were no cases in 1 005 participants who received the vaccine and 16 cases out of 978 who received placebo. The point

estimate for efficacy is 100% (95% confidence interval 75.3, 100.0). In participants with or without evidence of prior infection there were 0 cases in the 1 119 who received vaccine and 18 cases in 1 110 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 78.1, 100.0).

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

In the updated efficacy analysis of Study 2 in adolescents 12 to 15 years of age without evidence of prior infection, there were no cases in 1 057 participants who received the vaccine and 28 cases out of 1 030 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 86.8, 100.0) during the period when Alpha variant was the predominant circulating strain. In participants with or without evidence of prior infection there were 0 cases in the 1 119 who received vaccine and 30 cases in 1 109 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 87.5, 100.0).

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

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

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

Effectiveness of a booster dose of Comirnaty was based on an assessment of 50% neutralizing antibody titres (NT50) against SARS-CoV-2 (USA_WA1/2020) in Study 2. In this study, the booster dose was administered 5 to 8 months (median 7 months) after the second dose. In Study 2, analyses of NT50 1 month after the booster dose compared to 1 month after the primary series in individuals 18 through 55 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the booster vaccination demonstrated noninferiority for both geometric mean ratio (GMR) and difference in seroresponse rates. Seroresponse for a participant was defined as achieving a ≥ 4 -fold rise in NT50 from baseline (before primary series). These analyses are summarized in Table 6.

Table 6. SARS-CoV-2 neutralization assay - NT50 (titre)[†] (SARS-CoV-2 USA_WA1/2020) – GMT and seroresponse rate comparison of 1 month after booster dose to 1 month after primary series – participants 18 through 55 years of age without evidence of infection up to 1 month after booster dose* – booster dose evaluable immunogenicity population[±]

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

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

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

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

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

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

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

An interim efficacy analysis of Study 4, a placebo-controlled booster study performed in approximately 10 000 participants 16 years of age and older who were recruited from Study 2, evaluated confirmed COVID-19 cases accrued from at least 7 days after booster vaccination up to a data cut-off date of 5 October 2021, which represents a median of 2.5 months post-booster follow-up.

The booster dose was administered 5 to 13 months (median 11 months) after the second dose. Vaccine efficacy of the Comirnaty booster dose after the primary series relative to the placebo booster group who only received the primary series dose was assessed.

The relative vaccine efficacy information for participants 16 years of age and older without prior evidence of SARS-CoV-2 infection is presented in Table 7. 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 7. 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.

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

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).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Comirnaty in 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 neutralizing antibody responses were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in foetuses and offspring. There were no vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development. No Comirnaty data are available on vaccine placental transfer or excretion in milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened vial

Frozen vial

2 years when stored at -90 °C to -60 °C.

The vaccine will be received frozen at -90 °C to -60 °C. Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

When stored frozen at -90 °C to -60 °C, 10-vial packs of the vaccine can be thawed at 2 °C to 8 °C for 6 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed vial

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

- Upon moving the vaccine to 2 °C to 8 °C storage, the updated expiry date must be written on the outer carton and the vaccine should be used or discarded by the updated expiry date. The original expiry date should be crossed out.
- If the vaccine is received at 2 °C to 8 °C it should be stored at 2 °C to 8 °C. The expiry date on the outer carton should have been updated to reflect the refrigerated expiry date and the original expiry date should have been crossed out.

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

Thawed vials can be handled in room light conditions.

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

Handling of temperature excursions during refrigerated storage

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

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

Opened vial

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

6.4 Special precautions for storage

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

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

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

For storage conditions after thawing and first opening, see section 6.3.

6.5 Nature and contents of container

2.25 mL dispersion in a 2 mL clear multidose vial (type I glass) with a stopper (synthetic bromobutyl rubber) and a grey flip-off plastic cap with aluminium seal. Each vial contains 6 doses, see section 6.6.

Pack sizes: 10 vials or 195 vials

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Handling instructions prior to use

Comirnaty Original/Omicron BA.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 **grey plastic cap** and the product **name is Comirnaty Original/Omicron BA.1 (15/15 micrograms)/dose dispersion for injection** (12 years and older).
- If the vial has another product name on the label, please make reference to the Summary of Product Characteristics 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 6 hours to thaw. Ensure vials are completely thawed prior to use.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Preparation of 0.3 mL doses

- Gently mix by inverting vials 10 times prior to use. Do not shake.
- Prior to mixing, the thawed dispersion may contain white to off-white opaque amorphous particles.
- After mixing, the vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the vaccine if particulates or discolouration are present.
- Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
- Withdraw 0.3 mL of Comirnaty Original/Omicron BA.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 vial. Discard any unused vaccine 12 hours after first puncture.

Disposal

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1528/006
EU/1/20/1528/007

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 December 2020
Date of latest renewal: 10 October 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

▼ 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 Original/Omicron BA.4-5 (15/15 micrograms)/dose dispersion for injection
COVID-19 mRNA Vaccine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

This is a single dose or a multidose vial with a grey cap. Do not dilute prior to use.

One single dose vial contains 1 dose of 0.3 mL, see sections 4.2 and 6.6.

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

One dose (0.3 mL) contains 15 micrograms of tozinameran and 15 micrograms of famtozinameran, a COVID-19 mRNA Vaccine (nucleoside modified, embedded in lipid nanoparticles).

Tozinameran 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 (Original). Famtozinameran 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 BA.4-5).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersion for injection.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Comirnaty Original/Omicron BA.4-5 (15/15 micrograms)/dose dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 12 years of age and older.

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

4.2 Posology and method of administration

Posology

Individuals 12 years of age and older

Comirnaty Original/Omicron BA.4-5 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 Original/Omicron BA.4-5 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Severely immunocompromised aged 12 years and older

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

Paediatric population

There are paediatric formulations available for infants aged 6 months and above and children below 12 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.

Elderly population

No dose adjustment is required in elderly individuals ≥ 65 years of age.

Method of administration

Comirnaty Original/Omicron BA.4-5 (15/15 micrograms)/dose dispersion for injection should be administered intramuscularly (see section 6.6). Do not dilute prior to use.

The preferred site is the deltoid muscle of the upper arm.

Do not inject the vaccine intravascularly, subcutaneously or intradermally.

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

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

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

Single dose vials

Single dose vials of Comirnaty Original/Omicron BA.4-5 contain 1 dose of 0.3 mL of vaccine.

- Withdraw a single 0.3 mL dose of Comirnaty Original/Omicron BA.4-5.
- Discard vial and any excess volume.
- Do not pool excess vaccine from multiple vials.

Multidose vials

Multidose vials of Comirnaty Original/Omicron BA.4-5 contain 6 doses of 0.3 mL of vaccine. In order to extract 6 doses from a single vial, low dead-volume syringes and/or needles should be used. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial. Irrespective of the type of syringe and needle:

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Traceability

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

General recommendations

Hypersensitivity and anaphylaxis

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

Close observation for at least 15 minutes is recommended following vaccination. No further dose of the vaccine should be given to those who have experienced anaphylaxis after a prior dose of Comirnaty.

Myocarditis and pericarditis

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

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

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

Anxiety-related reactions

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

Concurrent illness

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

Thrombocytopenia and coagulation disorders

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

Immunocompromised individuals

The efficacy and safety of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of Comirnaty Original/Omicron BA.4-5 may be lower in immunocompromised individuals.

Duration of protection

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

Limitations of vaccine effectiveness

As with any vaccine, vaccination with Comirnaty Original/Omicron BA.4-5 may not protect all vaccine recipients. Individuals may not be fully protected until 7 days after their vaccination.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concomitant administration of Comirnaty Original/Omicron BA.4-5 with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

No data are available yet regarding the use of Comirnaty Original/Omicron BA.4-5 during pregnancy.

However, a large amount of observational data from pregnant women vaccinated with the initially approved Comirnaty vaccine during the second and third trimester have not shown an increase in adverse pregnancy outcomes. While data on pregnancy outcomes following vaccination during the first trimester are presently limited, no increased risk for miscarriage has been seen. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development (see section 5.3). Based on data available with other vaccine variants, Comirnaty Original/Omicron BA.4-5 can be used during pregnancy.

Breast-feeding

No data are available yet regarding the use of Comirnaty Original/Omicron BA.4-5 during breast-feeding.

However, no effects on the breastfed newborn/infant are anticipated since the systemic exposure of breast-feeding woman to the vaccine is negligible. Observational data from women who were breast-feeding after vaccination with the initially approved Comirnaty vaccine have not shown a risk for adverse effects in breastfed newborns/infants. Comirnaty Original/Omicron BA.4-5 can be used during breast-feeding.

Fertility

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

4.7 Effects on ability to drive and use machines

Comirnaty Original/Omicron BA.4-5 has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under section 4.8 may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of safety profile

The safety of Comirnaty Original/Omicron BA.4-5 is inferred from safety data from Comirnaty and Omicron adapted vaccines.

Comirnaty 30 mcg

Participants 16 years of age and older – after 2 doses

In Study 2, a total of 22 026 participants 16 years of age or older received at least 1 dose of Comirnaty and a total of 22 021 participants 16 years of age or older received placebo (including 138 and 145 adolescents 16 and 17 years of age in the vaccine and placebo groups, respectively). A total of 20 519 participants 16 years of age or older received 2 doses of Comirnaty.

At the time of the analysis of Study 2 with a data cut-off of 13 March 2021 for the placebo-controlled blinded follow-up period up to the participants' unblinding dates, a total of 25 651 (58.2%) participants (13 031 Comirnaty and 12 620 placebo) 16 years of age and older were followed up for ≥ 4 months after the second dose. This included a total of 15 111 (7 704 Comirnaty and 7 407 placebo) participants 16 to 55 years of age and a total of 10 540 (5 327 Comirnaty and 5 213 placebo) participants 56 years of age and older.

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

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

Adolescents 12 to 15 years of age – after 2 doses

In an analysis of long-term safety follow-up in Study 2, 2 260 adolescents (1 131 Comirnaty and 1 129 placebo) were 12 to 15 years of age. Of these, 1 559 adolescents (786 Comirnaty and 773 placebo) have been followed for ≥ 4 months after the second dose of Comirnaty.

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

Participants 12 years of age and older – after booster dose

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 (see section 5.1).

Omicron-adapted Comirnaty

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

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

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

Tabulated list of adverse reactions from clinical studies of Comirnaty and Comirnaty Original/Omicron BA.4-5 and post-authorisation experience of Comirnaty in individuals 12 years of age and older

Adverse reactions observed during clinical studies are listed below according to the following frequency categories: Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1\ 000$ to $< 1/100$), Rare ($\geq 1/10\ 000$ to $< 1/1\ 000$), Very rare ($< 1/10\ 000$), Not known (cannot be estimated from the available data).

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

System Organ Class	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
	Uncommon	Hyperhidrosis; night sweats

System Organ Class	Frequency	Adverse reactions
Skin and subcutaneous tissue disorder	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 ^h
General disorders and administration site conditions	Very common	Injection site pain; fatigue; chills; pyrexia ^f ; injection site swelling
	Common	Injection site redness
	Uncommon	Asthenia; malaise; injection site pruritus
	Not known	Extensive swelling of vaccinated limb ^d ; facial swelling ^g

- In participants 5 years of age and older, a higher frequency of lymphadenopathy was reported after a booster ($\leq 2.8\%$) dose than after primary ($\leq 0.9\%$) doses of the vaccine.
- The frequency category for urticaria and angioedema was rare.
- Through the clinical trial safety follow-up period to 14 November 2020, acute peripheral facial paralysis (or palsy) was reported by four participants in the COVID-19 mRNA Vaccine group. Onset was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.
- Adverse reaction determined post-authorisation.
- Refers to vaccinated arm.
- A higher frequency of pyrexia was observed after the second dose compared to the first dose.
- Facial swelling in vaccine recipients with a history of injection of dermatological fillers has been reported in the post-marketing phase.
- Most cases appeared to be non-serious and temporary in nature.

Description of selected adverse reactions

Myocarditis and pericarditis

The increased risk of myocarditis after vaccination with Comirnaty is highest in younger males (see section 4.4).

Two large European pharmacoepidemiological studies have estimated the excess risk in younger males following the second dose of Comirnaty. One study showed that in a period of 7 days after the second dose there were about 0.265 (95% CI 0.255 - 0.275) extra cases of myocarditis in 12-29 year old males per 10 000 compared to unexposed persons. In another study, in a period of 28 days after the second dose there were 0.56 (95% CI 0.37 - 0.74) extra cases of myocarditis in 16-24 year old males per 10 000 compared to unexposed persons.

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#) and include batch/Lot number if available.

4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vaccines, viral vaccines, ATC code: J07BN01

Mechanism of action

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

Efficacy

Omicron-adapted Comirnaty

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

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

Analyses of 50% neutralizing antibody titres (NT50) against Omicron BA.4-5 and against reference strain among participants 56 years of age and older who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 in Study 5 compared to a subset of participants from Study 4 who received a booster (fourth dose) of Comirnaty demonstrated superiority of Comirnaty Original/Omicron BA.4-5 to Comirnaty based on geometric mean ratio (GMR) and noninferiority based on difference in seroresponse rates with respect to anti-Omicron BA.4-5 response, and noninferiority of anti-reference strain immune response based on GMR (Table 2).

Analyses of NT50 against Omicron BA.4/BA.5 among participants 18 to 55 years of age compared to participants 56 years of age and older who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 in Study 5 demonstrated noninferiority of anti-Omicron BA.4-5 response among participants 18 to 55 years of age compared to participants 56 years of age and older for both GMR and difference in seroresponse rates (Table 2).

The study also assessed the level of NT50 of the anti-Omicron BA.4-5 SARS-CoV-2 and reference strains pre-vaccination and 1 month after vaccination in participants who received a booster (fourth dose) (Table 3).

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

SARS-CoV-2 GMTs (NT50) at 1 month after vaccination course								
SARS-CoV-2 neutralization assay	Study 5 Comirnaty Original/Omicron BA.4-5				Subset of Study 4 Comirnaty		Age group comparison	Vaccine group comparison
	18 through 55 years of age		56 years of age and older		56 years of age and older		Comirnaty Original/Omicron BA.4-5 18 through 55 years of age/≥ 56 years of age	≥ 56 years of age Comirnaty Original/Omicron BA.4-5 /Comirnaty
	n ^a	GMT ^c (95% CI ^c)	n ^a	GMT ^b (95% CI ^b)	n ^a	GMT ^b (95% CI ^b)	GMR ^c (95% CI ^c)	GMR ^c (95% CI ^c)
Omicron BA.4-5 - NT50 (titre) ^d	297	4 455.9 (3 851.7, 5 154.8)	284	4 158.1 (3 554.8, 4 863.8)	282	938.9 (802.3, 1 098.8)	0.98 (0.83, 1.16) ^e	2.91 (2.45, 3.44) ^f
Reference Strain – NT50 (titre) ^d	-	-	286	16 250.1 (14 499.2, 18 212.4)	289	10 415.5 (9 366.7, 11 581.8)	-	1.38 (1.22, 1.56) ^g
Difference in percentages of participants with seroresponse at 1 month after vaccination course								
SARS-CoV-2 neutralization assay	Comirnaty Original/Omicron BA.4-5				Subset of Study 4 Comirnaty		Age group comparison	Vaccine group comparison ≥ 56 years of age
	18 through 55 years of age		56 years of age and older		56 years of age and older		Comirnaty Original/Omicron BA.4-5 18 through 55 years of age/≥ 56	Comirnaty Original/Omicron BA.4-5 /Comirnaty
	N ^h	n ⁱ (%) (95% CI ^k)	N ^h	n ⁱ (%) (95% CI ^k)	N ^h	n ⁱ (%) (95% CI ^j)	Difference ^k (95% CI ^l)	Difference ^k (95% CI ^l)
Omicron BA.4-5 - NT50 (titre) ^d	294	180 (61.2) (55.4, 66.8)	282	188 (66.7) (60.8, 72.1)	273	127 (46.5) (40.5, 52.6)	-3.03 (-9.68, 3.63) ^m	26.77 (19.59, 33.95) ⁿ

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

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

- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the difference of LS means and corresponding CIs based on analysis of logarithmically transformed neutralizing titres using a linear regression model with terms of baseline neutralizing titre (log scale) and vaccine group or age group.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).
- Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67.
- Superiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 1.
- Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥ 0.8.

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

Table 3. Geometric mean titres – Comirnaty Original/Omicron BA.4-5 subsets of Study 5 – prior to and 1 month after booster (fourth dose) – participants 12 years of age and older – with or without evidence of infection - evaluable immunogenicity population

SARS-CoV-2 neutralization assay	Sampling time point ^a	Comirnaty Original/Omicron BA.4-5					
		12 through 17 years of age		18 through 55 years of age		56 years of age and older	
		n ^b	GMT ^c (95% CI ^c)	n ^b	GMT ^c (95% CI ^c)	n ^b	GMT ^c (95% CI ^c)
Omicron BA.4-5 - NT50 (titre) ^d	Pre-vaccination	104	1 105.8 (835.1, 1 464.3)	294	569.6 (471.4, 688.2)	284	458.2 (365.2, 574.8)
	1 month	105	8 212.8 (6 807.3, 9 908.7)	297	4 455.9 (3 851.7, 5 154.8)	284	4 158.1 (3 554.8, 4 863.8)
Reference Strain – NT50 (titre) ^d	Pre-vaccination	105	6 863.3 (5 587.8, 8 430.1)	296	4 017.3 (3 430.7, 4 704.1)	284	3 690.6 (3 082.2, 4 419.0)
	1 month	105	23 641.3 (20 473.1, 27 299.8)	296	16 323.3 (14 686.5, 18 142.6)	286	16 250.1 (14 499.2, 18 212.4)

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

- a. Protocol-specified timing for blood sample collection.
- b. n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
- d. SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4-5).

Comirnaty 30 mcg

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

Efficacy in participants 16 years of age and older – after 2 doses

In the Phase 2/3 portion of Study 2, based on data accrued through 14 November 2020, approximately 44 000 participants were randomised equally and were to receive 2 doses of the initially approved COVID-19 mRNA Vaccine or placebo. The efficacy analyses included participants that received their

second vaccination within 19 to 42 days after their first vaccination. The majority (93.1%) of vaccine recipients received the second dose 19 days to 23 days after Dose 1. Participants are planned to be followed for up to 24 months after Dose 2, for assessments of safety and efficacy against COVID-19. In the clinical study, participants were required to observe a minimum interval of 14 days before and after administration of an influenza vaccine in order to receive either placebo or COVID-19 mRNA Vaccine. In the clinical study, participants were required to observe a minimum interval of 60 days before or after receipt of blood/plasma products or immunoglobulins within through conclusion of the study in order to receive either placebo or COVID-19 mRNA Vaccine.

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

At the time of the primary efficacy analysis, participants had been followed for symptomatic COVID-19 for in total 2 214 person-years for the COVID-19 mRNA Vaccine and in total 2 222 person-years in the placebo group.

There were no meaningful clinical differences in overall vaccine efficacy in participants who were at risk of severe COVID-19 including those with 1 or more comorbidities that increase the risk of severe COVID-19 (e.g. asthma, body mass index (BMI) ≥ 30 kg/m², chronic pulmonary disease, diabetes mellitus, hypertension).

The vaccine efficacy information is presented in Table 4.

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

First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection*			
Subgroup	COVID-19 mRNA Vaccine N^a = 18 198 Cases n1^b Surveillance time^c (n2^d)	Placebo N^a = 18 325 Cases n1^b Surveillance time^c (n2^d)	Vaccine efficacy % (95% CI)^e
All participants	8 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.

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

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

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

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

The updated vaccine efficacy information is presented in Table 5.

Table 5. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of prior SARS-CoV-2 infection* prior to 7 days after Dose 2 – evaluable efficacy (7 days) population during the placebo-controlled follow-up period

Subgroup	COVID-19 mRNA Vaccine N ^a =20 998 Cases n1 ^b Surveillance time ^c (n2 ^d)	Placebo N ^a =21 096 Cases n1 ^b Surveillance time ^c (n2 ^d)	Vaccine efficacy % (95% CI ^e)
All participants ^f	77 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.

- N = Number of participants in the specified group.
- n1 = Number of participants meeting the endpoint definition.
- 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.
- n2 = Number of participants at risk for the endpoint.

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

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

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

Efficacy against severe COVID-19

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

As of 13 March 2021, vaccine efficacy against severe COVID-19 is presented only for participants with or without prior SARS-CoV-2 infection (Table 6) as the COVID-19 case counts in participants without prior SARS-CoV-2 infection were the same as those in participants with or without prior SARS-CoV-2 infection in both the COVID-19 mRNA Vaccine and placebo groups.

Table 6. Vaccine efficacy – First severe COVID-19 occurrence in participants with or without prior SARS-CoV-2 infection based on the Food and Drug Administration (FDA)* after Dose 1 or from 7 days after Dose 2 in the placebo-controlled follow-up

	COVID-19 mRNA Vaccine Cases n1 ^a Surveillance time (n2 ^b)	Placebo Cases n1 ^a Surveillance time (n2 ^b)	Vaccine efficacy % (95% CI ^c)
After Dose 1 ^d	1 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 $\leq 93\%$ on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen < 300 mm Hg);
- Respiratory failure [defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
- Evidence of shock (systolic blood pressure < 90 mm Hg, diastolic blood pressure < 60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an Intensive Care Unit;
- Death.

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

b. n2 = Number of participants at risk for the endpoint.

c. Two-side confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.

d. Efficacy assessed based on the Dose 1 all a available efficacy (modified intention-to-treat) population that included all randomised participants who received at least 1 dose of study intervention.

- e. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.
- f. Efficacy assessed based on the evaluable efficacy (7 Days) population that included all eligible randomised participants who receive all dose(s) of study intervention as randomised within the predefined window, have no other important protocol deviations as determined by the clinician.
- g. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

Efficacy and immunogenicity in adolescents 12 to 15 years of age – after 2 doses

In an initial analysis of Study 2 in adolescents 12 to 15 years of age (representing a median follow-up duration of > 2 months after Dose 2) without evidence of prior infection, there were no cases in 1 005 participants who received the vaccine and 16 cases out of 978 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 75.3, 100.0). In participants with or without evidence of prior infection there were 0 cases in the 1 119 who received vaccine and 18 cases in 1 110 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 78.1, 100.0).

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

In the updated efficacy analysis of Study 2 in adolescents 12 to 15 years of age without evidence of prior infection, there were no cases in 1 057 participants who received the vaccine and 28 cases out of 1 030 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 86.8, 100.0) during the period when Alpha variant was the predominant circulating strain. In participants with or without evidence of prior infection there were 0 cases in the 1 119 who received vaccine and 30 cases in 1 109 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 87.5, 100.0).

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

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

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

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

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

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

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

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

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

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

a. n = Number of participants with valid and determinate assay results at both sampling time points within specified window.

b. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.

c. GMRs and 2-sided 97.5% CIs were calculated by exponentiating the mean differences in the logarithms of the assay and the corresponding CIs (based on the Student t distribution).

d. Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the GMR is > 0.67 and the point estimate of the GMR is ≥ 0.80 .

e. n = Number of participants with valid and determinate assay results for the specified assay at baseline, 1 month after Dose 2 and 1 month after the booster dose within specified window. These values are the denominators for the percentage calculations.

f. Number of participants with seroresponse for the given assay at the given dose/sampling time point. Exact 2-sided CI based on the Clopper and Pearson method.

g. Difference in proportions, expressed as a percentage (1 month after booster dose – 1 month after Dose 2).

h. Adjusted Wald 2-sided CI for the difference in proportions, expressed as a percentage.

i. Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the percentage difference is $> -10\%$.

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

An interim efficacy analysis of Study 4, a placebo-controlled booster study performed in approximately 10 000 participants 16 years of age and older who were recruited from Study 2, evaluated confirmed COVID-19 cases accrued from at least 7 days after booster vaccination up to a data cut-off date of 5 October 2021, which represents a median of 2.5 months post-booster follow-up.

The booster dose was administered 5 to 13 months (median 11 months) after the second dose. Vaccine efficacy of the Comirnaty booster dose after the primary series relative to the placebo booster group who only received the primary series dose was assessed.

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

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

First COVID-19 occurrence from 7 days after booster dose in participants without evidence of prior SARS-CoV-2 infection*			
	Comirnaty N^a=4 695 Cases n1^b Surveillance Time^c (n2^d)	Placebo N^a=4 671 Cases n1^b Surveillance Time^c (n2^d)	Relative Vaccine Efficacy^e % (95% CI^f)
First COVID-19 occurrence from 7 days after booster vaccination	6 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.

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

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).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Comirnaty in 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 neutralizing antibody responses were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in foetuses and offspring. There were no vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development. No Comirnaty data are available on vaccine placental transfer or excretion in milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

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

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

Cholesterol

Trometamol

Trometamol hydrochloride

Sucrose

Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened vial

Frozen vial

2 years when stored at -90 °C to -60 °C.

The vaccine will be received frozen at -90 °C to -60 °C. Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

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 or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Multidose vials

When stored frozen at -90 °C to -60 °C, 10-vial packs of multidose vials of the vaccine can be thawed at 2 °C to 8 °C for 6 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed vial

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

- Upon moving the vaccine to 2 °C to 8 °C storage, the updated expiry date must be written on the outer carton and the vaccine should be used or discarded by the updated expiry date. The original expiry date should be crossed out.
- If the vaccine is received at 2 °C to 8 °C it should be stored at 2 °C to 8 °C. The expiry date on the outer carton should have been updated to reflect the refrigerated expiry date and the original expiry date should have been crossed out.

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

Thawed vials can be handled in room light conditions.

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

Handling of temperature excursions during refrigerated storage

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

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

Opened vial

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

6.4 Special precautions for storage

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

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

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

For storage conditions after thawing and first opening, see section 6.3.

6.5 Nature and contents of container

Comirnaty Original/Omicron BA.4-5 dispersion is supplied in a 2 mL clear vial (type I glass) with a stopper (synthetic bromobutyl rubber) and a grey flip-off plastic cap with aluminium seal.

One single dose vial contains 1 dose of 0.3 mL, see sections 4.2 and 6.6.

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

Single dose vial pack size: 10 vials.

Multidose vial pack sizes: 10 vials or 195 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Handling instructions prior to use

Comirnaty Original/Omicron BA.4-5 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- **Verify** that the vial has a **grey plastic cap** and the product **name is Comirnaty Original/Omicron BA.4-5 (15/15 micrograms)/dose dispersion for injection** (12 years and older).
- If the vial has another product name on the label, please make reference to the Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw. Ensure vials are completely thawed prior to use.
 - 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).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Preparation of 0.3 mL doses

- Gently mix by inverting vials 10 times prior to use. Do not shake.
- Prior to mixing, the thawed dispersion may contain white to off-white opaque amorphous particles.
- After mixing, the vaccine should present as a white to off-white 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 Original/Omicron BA.4-5.
- 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 vial. Discard any unused vaccine 12 hours after first puncture.

Disposal

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

Single dose vials

EU/1/20/1528/014

Multidose vials

EU/1/20/1528/008
 EU/1/20/1528/009

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 December 2020
 Date of latest renewal: 10 October 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

▼ 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 Original/Omicron BA.4-5 (5/5 micrograms)/dose concentrate for dispersion for injection
COVID-19 mRNA Vaccine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

One vial (1.3 mL) contains 10 doses of 0.2 mL after dilution, see sections 4.2 and 6.6.

One dose (0.2 mL) contains 5 micrograms of tozinameran and 5 micrograms of famtozinameran, a COVID-19 mRNA Vaccine (nucleoside modified, embedded in lipid nanoparticles).

Tozinameran 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 (Original). Famtozinameran 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 BA.4-5).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose concentrate for dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in children aged 5 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 Original/Omicron BA.4-5 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 Original/Omicron BA.4-5 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Severely immunocompromised aged 5 years and older

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

Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose should be used only for children 5 to 11 years of age.

Paediatric population

There are paediatric formulations available for infants and children aged 6 months to 4 years. For details, please refer to the 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 Original/Omicron BA.4-5 (5/5 micrograms)/dose concentrate for dispersion for injection should be administered intramuscularly after dilution (see section 6.6).

After dilution, vials of Comirnaty Original/Omicron BA.4-5 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.

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

The efficacy and safety of the vaccine has not been assessed in individuals with weakened immune systems, including those receiving immunosuppressant therapy. The efficacy of Comirnaty Original/Omicron BA.4-5 may be lower in individuals with weakened immune systems.

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 Original/Omicron BA.4-5 may not protect all vaccine recipients. Individuals may not be fully protected until 7 days after their vaccination.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concomitant administration of Comirnaty Original/Omicron BA.4-5 with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

No data are available yet regarding the use of Comirnaty Original/Omicron BA.4-5 during pregnancy.

However, a large amount of observational data from pregnant women vaccinated with the initially approved Comirnaty vaccine during the second and third trimester have not shown an increase in adverse pregnancy outcomes. While data on pregnancy outcomes following vaccination during the first trimester are presently limited, no increased risk for miscarriage has been seen. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development (see section 5.3). Based on data available with other vaccine variants, Comirnaty Original/Omicron BA.4-5 can be used during pregnancy.

Breast-feeding

No data are available yet regarding the use of Comirnaty Original/Omicron BA.4-5 during breast-feeding.

However, no effects on the breastfed newborn/infant are anticipated since the systemic exposure of breast-feeding woman to the vaccine is negligible. Observational data from women who were breast-feeding after vaccination with the initially approved Comirnaty vaccine have not shown a risk for adverse effects in breastfed newborns/infants. Comirnaty Original/Omicron BA.4-5 can be used during breast-feeding.

Fertility

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

4.7 Effects on ability to drive and use machines

Comirnaty Original/Omicron BA.4-5 has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under section 4.8 may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of safety profile

The safety of Comirnaty Original/Omicron BA.4-5 is inferred from safety data from Comirnaty and Omicron adapted vaccines.

Comirnaty

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

In Study 3, a total of 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 ($\geq 20\%$), myalgia, chills, and diarrhoea ($> 10\%$).

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

In a subset from Study 3, a total of 401 children 5 to 11 years of age received a booster dose of Comirnaty 10 mcg at least 5 months (range of 5 to 9 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 22 March 2022 (median follow-up time of 1.3 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 were injection site pain (> 70%), fatigue (> 40%), headache (> 30%), 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 \geq 4 months after the second dose.

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

Participants 16 years of age and older – after 2 doses

In Study 2, a total of 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 \geq 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 \geq 6 months after the booster dose to the cut-off date (22 November 2021).

The overall safety profile for the booster dose was similar to that seen after 2 doses. The most frequent adverse reactions in participants 18 to 55 years of age were injection site pain (> 80%), fatigue (> 60%), headache (> 40%), myalgia (> 30%), chills and arthralgia (> 20%).

In Study 4, a placebo-controlled booster study, participants 16 years of age and older recruited from Study 2 received a booster dose of Comirnaty (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

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

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

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

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

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

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

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

Adverse reactions observed during clinical studies are listed below according to the following frequency categories: Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1\ 000$ to $< 1/100$), Rare ($\geq 1/10\ 000$ to $< 1/1\ 000$), Very rare ($< 1/10\ 000$), Not known (cannot be estimated from the available data).

Table 1. Adverse reactions from Comirnaty 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
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

- In participants 5 years of age and older, a higher frequency of lymphadenopathy was reported after a booster ($\leq 2.8\%$) dose than after primary ($\leq 0.9\%$) doses of the vaccine.
- The frequency category for urticaria and angioedema was rare.
- Through the clinical trial safety follow-up period to 14 November 2020, acute peripheral facial paralysis (or palsy) was reported by four participants in the COVID-19 mRNA Vaccine group. Onset was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.
- Adverse reaction determined post-authorisation.
- Refers to vaccinated arm.
- A higher frequency of pyrexia was observed after the second dose compared to the first dose.
- Facial swelling in vaccine recipients with a history of injection of dermatological fillers has been reported in the post-marketing phase.
- Injection site redness occurred at a higher frequency (very common) in children 5 to 11 years of age.
- Most cases appeared to be non-serious and temporary in nature.

Description of selected adverse reactions

Myocarditis and pericarditis

The increased risk of myocarditis after vaccination with Comirnaty is highest in younger males (see section 4.4).

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 listed in [Appendix V](#) and include batch/Lot number if available.

4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vaccines, viral vaccines, ATC code: J07BN01

Mechanism of action

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

Efficacy

Omicron-adapted Comirnaty

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

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

The immune response 1 month after a booster dose (fourth dose), Comirnaty Original/Omicron BA.4-5 elicited generally similar Omicron BA.4/BA.5-specific neutralizing titres compared with the titres in the comparator group who received 3 doses of Comirnaty. Comirnaty Original/Omicron BA.4-5 also elicited similar reference strain-specific titres compared with the titres in the comparator group.

The vaccine immunogenicity results after a booster dose in participants 5 to 11 years of age are presented in Table 2.

Table 2. Study 6 – Geometric mean ratio and Geometric mean titres – participants with or without evidence of infection – 5 to 11 years of age – evaluable immunogenicity population

SARS-CoV-2 neutralization assay	Sampling time point ^a	Vaccine Group (as Assigned/Randomized)				
		Study 6 Comirnaty (Original/Omicron BA.4/BA.5) 10 mcg Dose 4 and 1 Month After Dose 4		Study 3 Comirnaty 10 mcg Dose 3 and 1 Month After Dose 3		Study 6 Comirnaty (Original/Omicron BA.4/BA.5)/Comirnaty 10 mcg
		n ^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% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
- GMRs and 2-sided CIs were calculated by exponentiating the difference of LS Means for the assay and the corresponding CIs based on an analysis of log-transformed assay results using a linear regression model with baseline log-transformed neutralizing titers, postbaseline infection status, and vaccine group as covariates.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).

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

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

Analyses of 50% neutralizing antibody titres (NT50) against Omicron BA.4-5 and against reference strain among participants 56 years of age and older who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 in Study 5 compared to a subset of participants from Study 4 who received a booster (fourth dose) of Comirnaty demonstrated superiority of Comirnaty Original/Omicron BA.4-5 to Comirnaty based on geometric mean ratio (GMR) and noninferiority based on difference in seroresponse rates with respect to anti-Omicron BA.4-5 response, and noninferiority of anti-reference strain immune response based on GMR (Table 3).

Analyses of NT50 against Omicron BA.4/BA.5 among participants 18 through 55 years of age compared to participants 56 years of age and older who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 in Study 5 demonstrated noninferiority of anti-Omicron BA.4-5 response among participants 18 through 55 years of age compared to participants 56 years of age and older for both GMR and difference in seroresponse rates (Table 3).

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

Table 3. SARS-CoV-2 GMTs (NT50) and difference in percentages of participants with seroresponse at 1 month after vaccination course – Comirnaty Original/Omicron BA.4-5 from Study 5 and Comirnaty from subset of Study 4 – participants with or without evidence of SARS-CoV-2 infection – evaluable immunogenicity population

SARS-CoV-2 GMTs (NT50) at 1 month after vaccination course								
SARS-CoV-2 neutralization assay	Study 5 Comirnaty Original/Omicron BA.4-5				Subset of Study 4 Comirnaty		Age group comparison	Vaccine group comparison
	18 through 55 years of age		56 years of age and older		56 years of age and older		Comirnaty Original/Omicron BA.4-5 18 through 55 years of age/≥ 56 years of age	≥ 56 years of age Comirnaty Original/Omicron BA.4-5 /Comirnaty
	n ^a	GMT ^c (95% CI ^c)	n ^a	GMT ^b (95% CI ^b)	n ^a	GMT ^b (95% CI ^b)	GMR ^c (95% CI ^c)	GMR ^c (95% CI ^c)
Omicron BA.4-5 - NT50 (titre) ^d	297	4 455.9 (3 851.7, 5 154.8)	284	4 158.1 (3 554.8, 4 863.8)	282	938.9 (802.3, 1 098.8)	0.98 (0.83, 1.16) ^e	2.91 (2.45, 3.44) ^f
Reference Strain – NT50 (titre) ^d	-	-	286	16 250.1 (14 499.2, 18 212.4)	289	10 415.5 (9 366.7, 11 581.8)	-	1.38 (1.22, 1.56) ^g
Difference in percentages of participants with seroresponse at 1 month after vaccination course								
SARS-CoV-2 neutralization assay	Comirnaty Original/Omicron BA.4-5				Subset of Study 4 Comirnaty		Age group comparison	Vaccine group comparison
	18 through 55 years of age		56 years of age and older		56 years of age and older		Comirnaty Original/Omicron BA.4-5 18 through 55 years of age/≥ 56	Comirnaty Original/Omicron BA.4-5 /Comirnaty
	N ^h	n ⁱ (%) (95% CI ^k)	N ^h	n ⁱ (%) (95% CI ^k)	N ^h	n ⁱ (%) (95% CI ^k)	Difference ^k (95% CI ^l)	Difference ^k (95% CI ^l)
Omicron BA.4-5 - NT50 (titre) ^d	294	180 (61.2) (55.4, 66.8)	282	188 (66.7) (60.8, 72.1)	273	127 (46.5) (40.5, 52.6)	-3.03 (-9.68, 3.63) ^m	26.77 (19.59, 33.95) ⁿ

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

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

- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the difference of LS means and corresponding CIs based on analysis of logarithmically transformed neutralizing titres using a linear regression model with terms of baseline neutralizing titre (log scale) and vaccine group or age group.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).

- e. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67.
- f. Superiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 1.
- g. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥ 0.8 .
- h. N = Number of participants with valid and determinate assay results for the specified assay at both the prevaccination time point and the given sampling time point. This value is the denominator for the percentage calculation.
- i. n = Number of participants with seroresponse for the given assay at the given sampling time point.
- j. Exact 2-sided CI, based on the Clopper and Pearson method.
- k. Difference in proportions, expressed as a percentage.
- l. 2-sided CI based on the Miettinen and Nurminen method stratified by baseline neutralizing titre category (< median, \geq median) for the difference in proportions. The median of baseline neutralizing titres was calculated based on the pooled data in 2 comparator groups.
- m. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is $> -10\%$.
- n. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is $> -5\%$.

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

SARS-CoV-2 neutralization assay	Sampling time point ^a	Comirnaty Original/Omicron BA.4-5					
		12 through 17 years of age		18 through 55 years of age		56 years of age and older	
		n ^b	GMT ^c (95% CI ^c)	n ^b	GMT ^c (95% CI ^c)	n ^b	GMT ^c (95% CI ^c)
Omicron BA.4-5 - NT50 (titre) ^d	Pre-vaccination	104	1 105.8 (835.1, 1 464.3)	294	569.6 (471.4, 688.2)	284	458.2 (365.2, 574.8)
	1 month	105	8 212.8 (6 807.3, 9 908.7)	297	4 455.9 (3 851.7, 5 154.8)	284	4 158.1 (3 554.8, 4 863.8)
Reference Strain – NT50 (titre) ^d	Pre-vaccination	105	6 863.3 (5 587.8, 8 430.1)	296	4 017.3 (3 430.7, 4 704.1)	284	3 690.6 (3 082.2, 4 419.0)
	1 month	105	23 641.3 (20 473.1, 27 299.8)	296	16 323.3 (14 686.5, 18 142.6)	286	16 250.1 (14 499.2, 18 212.4)

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

- a. Protocol-specified timing for blood sample collection.
- b. n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
- d. SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4-5).

Comirnaty

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

Efficacy in participants 16 years of age and older – after 2 doses

In the Phase 2/3 portion of Study 2, based on data accrued through 14 November 2020, approximately 44 000 participants were randomised equally and were to receive 2 doses of the initially approved COVID-19 mRNA Vaccine or placebo. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. The majority (93.1%) of vaccine recipients received the second dose 19 days to 23 days after Dose 1. Participants are planned to be followed for up to 24 months after Dose 2, for assessments of safety and efficacy against COVID-19. In the clinical study, participants were required to observe a minimum interval of 14 days before and after administration of an influenza vaccine in order to receive either placebo or COVID-19 mRNA Vaccine. In the clinical study, participants were required to observe a minimum interval of 60 days before or after receipt of blood/plasma products or immunoglobulins within through conclusion of the study in order to receive either placebo or COVID-19 mRNA Vaccine.

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

At the time of the primary efficacy analysis, participants had been followed for symptomatic COVID-19 for in total 2 214 person-years for the COVID-19 mRNA Vaccine and in total 2 222 person-years in the placebo group.

There were no meaningful clinical differences in overall vaccine efficacy in participants who were at risk of severe COVID-19 including those with 1 or more comorbidities that increase the risk of severe COVID-19 (e.g. asthma, body mass index (BMI) ≥ 30 kg/m², chronic pulmonary disease, diabetes mellitus, hypertension).

The vaccine efficacy information is presented in Table 5.

Table 5. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of infection prior to 7 days after Dose 2 – evaluable efficacy (7 days) population

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 n^{1b} Surveillance time^c (n^{2d})	Placebo N^a = 18 325 Cases n^{1b} Surveillance time^c (n^{2d})	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 6.

Table 6. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of prior SARS-CoV-2 infection* prior to 7 days after Dose 2 – evaluable efficacy (7 days) population during the placebo-controlled follow-up period

Subgroup	COVID-19 mRNA Vaccine 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 7) as the COVID-19 case counts in participants without prior SARS-CoV-2 infection were the same as those in participants with or without prior SARS-CoV-2 infection in both the COVID-19 mRNA Vaccine and placebo groups.

Table 7. Vaccine efficacy – First severe COVID-19 occurrence in participants with or without prior SARS-CoV-2 infection based on the Food and Drug Administration (FDA)* after Dose 1 or from 7 days after Dose 2 in the placebo-controlled follow-up

	COVID-19 mRNA Vaccine 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 $\leq 93\%$ on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen < 300 mm Hg);
- Respiratory failure [defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
- Evidence of shock (systolic blood pressure < 90 mm Hg, diastolic blood pressure < 60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an Intensive Care Unit;
- Death.

- a. n1 = Number of participants meeting the endpoint definition.
- b. n2 = Number of participants at risk for the endpoint.

- c. Two-side confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
- d. Efficacy assessed based on the Dose 1 all available efficacy (modified intention-to-treat) population that included all randomised participants who received at least 1 dose of study intervention.
- e. Total surveillance time in 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 8. No cases of COVID-19 were observed in either the vaccine group or the placebo group in participants with evidence of prior SARS-CoV-2 infection.

Table 8. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2: Without evidence of infection prior to 7 days after Dose 2 – Phase 2/3 – Children 5 to 11 years of age evaluable efficacy population

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 prespecified immunobridging criteria for both the geometric mean ratio (GMR) and the seroresponse difference with seroresponse defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from baseline (before Dose 1).

The GMR of the SARS-CoV-2 NT50 1 month after Dose 2 in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) to that of young adults 16 to 25 years of age was 1.04 (2-sided 95% CI: 0.93, 1.18). Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, 99.2% of children 5 to 11 years of age and 99.2% of participants 16 to 25 years of age had a seroresponse at 1 month after Dose 2. The difference in proportions of participants who had seroresponse between the 2 age groups (children – young adult) was 0.0% (2-sided 95% CI: -2.0%, 2.2%). This information is presented in Table 9.

Table 9. Summary of geometric mean ratio for 50% neutralising titre and difference in percentages of participants with seroresponse – comparison of children 5 to 11 years of age (Study 3) to participants 16 to 25 years of age (Study 2) – participants without evidence of infection up to 1 month after Dose 2 – immunobridging subset – Phase 2/3 – evaluable immunogenicity population

		COVID-19 mRNA Vaccine		5 to 11 years/ 16 to 25 years	
		10 mcg/dose 5 to 11 years N ^a =264	30 mcg/dose 16 to 25 years N ^a =253		
	Time point ^b	GMT ^c (95% CI ^e)	GMT ^c (95% CI ^e)	GMR ^d (95% CI ^d)	Met immunobridging objective ^e (Y/N)
Geometric mean 50% neutralizing 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% neutralizing 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 postvaccination assay result $\geq 4 \times$ LLOQ is considered a seroresponse.

- N = Number of participants with valid and determinate assay results before vaccination and at 1 month after Dose 2. These values are also the denominators used in the percentage calculations for seroresponse rates.
- Protocol-specified timing for blood sample collection.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (5 to 11 years of age minus 16 to 25 years of age) and the corresponding CI (based on the Student t distribution).
- Immunobridging based on GMT is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥ 0.8 .
- SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralisation is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralised.
- n = Number of participants with seroresponse based on NT50 1 month after Dose 2.
- Exact 2-sided CI based on the Clopper and Pearson method.
- Difference in proportions, expressed as a percentage (5 to 11 years of age minus 16 to 25 years of age).
- 2-Sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
- Immunobridging based on seroresponse rate is declared if the lower bound of the 2-sided 95% CI for the seroresponse difference is greater than -10.0%.

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

A booster dose of Comirnaty was given to 401 randomly selected participants in Study 3. Effectiveness of a booster dose in ages 5 to 11 is inferred by immunogenicity. The immunogenicity of this was assessed through NT50 against the reference strain of SARS-CoV-2 (USA_WA1/2020). Analyses of NT50 1 month after the booster dose compared to before the booster dose demonstrated a substantial increase in GMTs in individuals 5 through 11 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the dose 2 and the booster dose. This analysis is summarized in Table 10.

Table 10. Summary of geometric mean titres – NT50 – participants without evidence of infection – phase 2/3 – immunogenicity set – 5 through 11 years of age – evaluable immunogenicity population

Assay	Sampling time point ^a		1 month after booster dose/ 1 month after dose 2
	1 month after booster dose (n ^b =67)	1 month after dose 2 (n ^b =96)	
	GMT ^c (95% CI ^c)	GMT ^c (95% CI ^c)	GMR ^d (95% CI ^d)
SARS-CoV-2 neutralization 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% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

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

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Comirnaty in 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 neutralizing antibody responses were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in foetuses and offspring. There were no vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development. No Comirnaty data are available on vaccine placental transfer or excretion in milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

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

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

Cholesterol

Trometamol

Trometamol hydrochloride

Sucrose

Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial

Frozen vial

2 years when stored at -90 °C to -60 °C.

The vaccine will be received frozen at -90 °C to -60 °C. Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

When stored frozen at -90 °C to -60 °C, 10-vial packs of the vaccine can be thawed at 2 °C to 8 °C for 4 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed vial

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

- Upon moving the vaccine to 2 °C to 8 °C storage, the updated expiry date must be written on the outer carton and the vaccine should be used or discarded by the updated expiry date. The original expiry date should be crossed out.

- If the vaccine is received at 2 °C to 8 °C it should be stored at 2 °C to 8 °C. The expiry date on the outer carton should have been updated to reflect the refrigerated expiry date and the original expiry date should have been crossed out.

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

Thawed vials can be handled in room light conditions.

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

Handling of temperature excursions during refrigerated storage

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

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

Diluted medicinal product

Chemical and physical in-use stability has been demonstrated for 12 hours at 2 °C to 30 °C, after dilution with sodium chloride 9 mg/mL (0.9%) solution for injection, which includes up to 6 hours transportation time. From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

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

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

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

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

6.5 Nature and contents of container

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 sizes: 10 vials or 195 vials

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Handling instructions prior to use

Comirnaty Original/Omicron BA.4-5 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- **Verify that the vial has an orange plastic cap and the product name is Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose concentrate for dispersion for injection (children 5 to 11 years).**

- If the vial has another product name on the label, please make reference to the Summary of Product Characteristics 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 4 hours to thaw. Ensure vials are completely thawed prior to use.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Dilution

- 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 **1.3 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 1.3 mL air into the empty diluent syringe.
- Gently invert the diluted dispersion 10 times. Do not shake.
- The diluted vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discolouration are present.
- The diluted vials should be marked with the appropriate **discard date and time**.
- **After dilution**, store at 2 °C to 30 °C and use within **12 hours**.
- Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.

Preparation of 0.2 mL doses

- 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 Original/Omicron BA.4-5 for children aged 5 to 11 years. **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 12 hours after dilution.

Disposal

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

7. MARKETING AUTHORISATION HOLDER

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55131 Mainz
Germany
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Fax: +49 6131 9084-2121
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8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1528/011
EU/1/20/1528/012

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 December 2020
Date of latest renewal: 10 October 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

▼ 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 Original/Omicron BA.4-5 (5/5 micrograms)/dose dispersion for injection
COVID-19 mRNA Vaccine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

One single dose vial contains 1 dose of 0.3 mL, see sections 4.2 and 6.6.

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

One dose (0.3 mL) contains 5 micrograms of tozinameran and 5 micrograms of famtozinameran, a COVID-19 mRNA Vaccine (nucleoside modified, embedded in lipid nanoparticles).

Tozinameran 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 (Original). Famtozinameran 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 BA.4-5).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersion for injection.

The vaccine is a clear to slightly opalescent frozen dispersion (pH: 6.9 - 7.9).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in children aged 5 to 11 years.

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 Original/Omicron BA.4-5 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 Original/Omicron BA.4-5 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Severely immunocompromised aged 5 years and older

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

Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose should be used only for children 5 to 11 years of age.

Paediatric population

There are paediatric formulations available for infants and children aged 6 months to 4 years. For details, please refer to the 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 Original/Omicron BA.4-5 (5/5 micrograms)/dose dispersion for injection should be administered intramuscularly (see section 6.6). Do not dilute prior to use.

The preferred site is the deltoid muscle of the upper arm.

Do not inject the vaccine intravascularly, subcutaneously or intradermally.

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

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

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

Single dose vials

Single dose vials of Comirnaty Original/Omicron BA.4-5 contain 1 dose of 0.3 mL of vaccine.

- Withdraw a single 0.3 mL dose of Comirnaty Original/Omicron BA.4-5.
- Discard vial and any excess volume.
- Do not pool excess vaccine from multiple vials.

Multidose vials

Multidose vials of Comirnaty Original/Omicron BA.4-5 contain 6 doses of 0.3 mL of vaccine. In order to extract 6 doses from a single vial, low dead-volume syringes and/or needles should be used. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial. Irrespective of the type of syringe and needle:

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Traceability

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

General recommendations

Hypersensitivity and anaphylaxis

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

Close observation for at least 15 minutes is recommended following vaccination. No further dose of the vaccine should be given to those who have experienced anaphylaxis after a prior dose of Comirnaty.

Myocarditis and pericarditis

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

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

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

Anxiety-related reactions

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

Concurrent illness

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

Thrombocytopenia and coagulation disorders

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

Immunocompromised individuals

The efficacy and safety of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of Comirnaty Original/Omicron BA.4-5 may be lower in immunocompromised individuals.

Duration of protection

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

Limitations of vaccine effectiveness

As with any vaccine, vaccination with Comirnaty Original/Omicron BA.4-5 may not protect all vaccine recipients. Individuals may not be fully protected until 7 days after their vaccination.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concomitant administration of Comirnaty Original/Omicron BA.4-5 with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

No data are available yet regarding the use of Comirnaty Original/Omicron BA.4-5 during pregnancy.

However, a large amount of observational data from pregnant women vaccinated with the initially approved Comirnaty vaccine during the second and third trimester have not shown an increase in adverse pregnancy outcomes. While data on pregnancy outcomes following vaccination during the first trimester are presently limited, no increased risk for miscarriage has been seen. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development (see section 5.3). Based on data available with other vaccine variants, Comirnaty Original/Omicron BA.4-5 can be used during pregnancy.

Breast-feeding

No data are available yet regarding the use of Comirnaty Original/Omicron BA.4-5 during breast-feeding.

However, no effects on the breastfed newborn/infant are anticipated since the systemic exposure of breast-feeding woman to the vaccine is negligible. Observational data from women who were breast-feeding after vaccination with the initially approved Comirnaty vaccine have not shown a risk for adverse effects in breastfed newborns/infants. Comirnaty Original/Omicron BA.4-5 can be used during breast-feeding.

Fertility

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

4.7 Effects on ability to drive and use machines

Comirnaty Original/Omicron BA.4-5 has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under section 4.8 may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of safety profile

The safety of Comirnaty Original/Omicron BA.4-5 is inferred from safety data from Comirnaty and Omicron adapted vaccines.

Comirnaty

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

In Study 3, a total of 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 ($\geq 20\%$), myalgia, chills, and diarrhoea ($> 10\%$).

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

In a subset from Study 3, a total of 401 children 5 to 11 years of age received a booster dose of Comirnaty 10 mcg at least 5 months (range of 5 to 9 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 22 March 2022 (median follow-up time of 1.3 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 were injection site pain ($> 70\%$), fatigue ($> 40\%$), headache ($> 30\%$), 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

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

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

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

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

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

The overall safety profile for the Comirnaty Original/Omicron BA.4-5 booster (fourth dose) was similar to that seen after 3 doses. The most frequent adverse reactions in participants 12 years of age

and older were injection site pain (> 60%), fatigue (> 50%), headache (> 40%), muscle pain (> 20%), chills (> 10%), and joint pain (> 10%).

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

Adverse reactions observed during clinical studies are listed below according to the following frequency categories: Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1\ 000$ to $< 1/100$), Rare ($\geq 1/10\ 000$ to $< 1/1\ 000$), Very rare ($< 1/10\ 000$), Not known (cannot be estimated from the available data).

Table 1. Adverse reactions from Comirnaty 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
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

- In participants 5 years of age and older, a higher frequency of lymphadenopathy was reported after a booster ($\leq 2.8\%$) dose than after primary ($\leq 0.9\%$) doses of the vaccine.
- The frequency category for urticaria and angioedema was rare.
- Through the clinical trials safety follow-up period to 14 November 2020, acute peripheral facial paralysis (or palsy) was reported by four participants in the COVID-19 mRNA Vaccine group. Onset was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.
- Adverse reaction determined post-authorisation.
- Refers to vaccinated arm.
- A higher frequency of pyrexia was observed after the second dose compared to the first dose.
- Facial swelling in vaccine recipients with a history of injection of dermatological fillers has been reported in the post-marketing phase.
- Injection site redness occurred at a higher frequency (very common) in children 5 to 11 years of age.
- Most cases appeared to be non-serious and temporary in nature.

Description of selected adverse reactions

Myocarditis and pericarditis

The increased risk of myocarditis after vaccination with Comirnaty is highest in younger males (see section 4.4).

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 listed in [Appendix V](#) and include batch/Lot number if available.

4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vaccines, viral vaccines, ATC code: J07BN01

Mechanism of action

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

Efficacy

Omicron-adapted Comirnaty

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

In an analysis of a subset from Study 6, 103 participants 5 to 11 years of age who had previously received a 2-dose primary series and booster dose with Comirnaty received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5. Results include immunogenicity data from a comparator subset

of participants 5 to 11 years of age in Study 3 who received 3 doses of Comirnaty. In participants 5 to 11 years of age who received a fourth dose of Comirnaty Original/Omicron BA.4-5 and participants 5 to 11 years of age who received a third dose of Comirnaty, 57.3% and 58.4% were positive for SARS-CoV-2 at baseline, respectively.

The immune response 1 month after a booster dose (fourth dose), Comirnaty Original/Omicron BA.4-5 elicited generally similar Omicron BA.4/BA.5-specific neutralizing titres compared with the titres in the comparator group who received 3 doses of Comirnaty. Comirnaty Original/Omicron BA.4-5 also elicited similar reference strain-specific titres compared with the titres in the comparator group.

The vaccine immunogenicity results after a booster dose in participants 5 to 11 years of age are presented in Table 2.

Table 2. Study 6 – Geometric mean ratio and Geometric mean titres – participants with or without evidence of infection – 5 to 11 years of age – evaluable immunogenicity population

SARS-CoV-2 neutralization assay	Sampling time point ^a	Vaccine Group (as Assigned/Randomized)				
		Study 6 Comirnaty (Original/Omicron BA.4/BA.5) 10 mcg Dose 4 and 1 Month After Dose 4		Study 3 Comirnaty 10 mcg Dose 3 and 1 Month After Dose 3		Study 6 Comirnaty (Original/Omicron BA.4/BA.5)/Comirnaty 10 mcg
		n ^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% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
- GMRs and 2-sided CIs were calculated by exponentiating the difference of LS Means for the assay and the corresponding CIs based on an analysis of log-transformed assay results using a linear regression model with baseline log-transformed neutralizing titers, postbaseline infection status, and vaccine group as covariates.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).

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

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

Analyses of 50% neutralizing antibody titres (NT50) against Omicron BA.4-5 and against reference strain among participants 56 years of age and older who received a booster (fourth dose) of Comirnaty

Original/Omicron BA.4-5 in Study 5 compared to a subset of participants from Study 4 who received a booster (fourth dose) of Comirnaty demonstrated superiority of Comirnaty Original/Omicron BA.4-5 to Comirnaty based on geometric mean ratio (GMR) and noninferiority based on difference in seroresponse rates with respect to anti-Omicron BA.4-5 response, and noninferiority of anti-reference strain immune response based on GMR (Table 3).

Analyses of NT50 against Omicron BA.4/BA.5 among participants 18 through 55 years of age compared to participants 56 years of age and older who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 in Study 5 demonstrated noninferiority of anti-Omicron BA.4-5 response among participants 18 through 55 years of age compared to participants 56 years of age and older for both GMR and difference in seroresponse rates (Table 3).

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

Table 3. SARS-CoV-2 GMTs (NT50) and difference in percentages of participants with seroresponse at 1 month after vaccination course – Comirnaty Original/Omicron BA.4-5 from Study 5 and Comirnaty from subset of Study 4 – participants with or without evidence of SARS-CoV-2 infection – evaluable immunogenicity population

SARS-CoV-2 GMTs (NT50) at 1 month after vaccination course								
SARS-CoV-2 neutralization assay	Study 5 Comirnaty Original/Omicron BA.4-5				Subset of Study 4 Comirnaty		Age group comparison	Vaccine group comparison
	18 through 55 years of age		56 years of age and older		56 years of age and older		Comirnaty Original/Omicron BA.4-5 18 through 55 years of age/≥ 56 years of age	≥ 56 years of age Comirnaty Original/Omicron BA.4-5 /Comirnaty
	n ^a	GMT ^c (95% CI ^c)	n ^a	GMT ^b (95% CI ^b)	n ^a	GMT ^b (95% CI ^b)	GMR ^c (95% CI ^c)	GMR ^c (95% CI ^c)
	Omicron BA.4-5 - NT50 (titre) ^d	297	4 455.9 (3 851.7, 5 154.8)	284	4 158.1 (3 554.8, 4 863.8)	282	938.9 (802.3, 1 098.8)	0.98 (0.83, 1.16) ^e
Reference Strain – NT50 (titre) ^d	-	-	286	16 250.1 (14 499.2, 18 212.4)	289	10 415.5 (9 366.7, 11 581.8)	-	1.38 (1.22, 1.56) ^g
Difference in percentages of participants with seroresponse at 1 month after vaccination course								
SARS-CoV-2 neutralization assay	Comirnaty Original/Omicron BA.4-5				Subset of Study 4 Comirnaty		Age group comparison	Vaccine group comparison
	18 through 55 years of age		56 years of age and older		56 years of age and older		Comirnaty Original/Omicron BA.4-5 18 through 55 years of age/≥ 56	Comirnaty Original/Omicron BA.4-5 /Comirnaty
	N ^h	n ⁱ (%) (95% CI ^k)	N ^h	n ⁱ (%) (95% CI ^k)	N ^h	n ⁱ (%) (95% CI ^l)	Difference ^k (95% CI ^l)	Difference ^k (95% CI ^l)
	Omicron BA.4-5 - NT50 (titre) ^d	294	180 (61.2) (55.4, 66.8)	282	188 (66.7) (60.8, 72.1)	273	127 (46.5) (40.5, 52.6)	-3.03 (-9.68, 3.63) ^m

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

Note: Seroreponse is defined as achieving a ≥ 4 -fold rise from baseline. If the baseline measurement is below the LLOQ, a postvaccination assay result $\geq 4 \times$ LLOQ is considered a seroreponse.

- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the difference of LS means and corresponding CIs based on analysis of logarithmically transformed neutralizing titres using a linear regression model with terms of baseline neutralizing titre (log scale) and vaccine group or age group.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).
- Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67.
- Superiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 1.
- Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥ 0.8 .
- N = Number of participants with valid and determinate assay results for the specified assay at both the prevaccination time point and the given sampling time point. This value is the denominator for the percentage calculation.
- n = Number of participants with seroreponse for the given assay at the given sampling time point.
- Exact 2-sided CI, based on the Clopper and Pearson method.
- Difference in proportions, expressed as a percentage.
- 2-sided CI based on the Miettinen and Nurminen method stratified by baseline neutralizing titre category ($<$ median, \geq median) for the difference in proportions. The median of baseline neutralizing titres was calculated based on the pooled data in 2 comparator groups.
- Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroreponse is $> -10\%$.
- Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroreponse is $> -5\%$.

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

SARS-CoV-2 neutralization assay	Sampling time point ^a	Comirnaty Original/Omicron BA.4-5					
		12 through 17 years of age		18 through 55 years of age		56 years of age and older	
		n ^b	GMT ^c (95% CI ^e)	n ^b	GMT ^c (95% CI ^e)	n ^b	GMT ^c (95% CI ^e)
Omicron BA.4-5 - NT50 (titre) ^d	Pre-vaccination	104	1 105.8 (835.1, 1 464.3)	294	569.6 (471.4, 688.2)	284	458.2 (365.2, 574.8)
	1 month	105	8 212.8 (6 807.3, 9 908.7)	297	4 455.9 (3 851.7, 5 154.8)	284	4 158.1 (3 554.8, 4 863.8)
Reference Strain – NT50 (titre) ^d	Pre-vaccination	105	6 863.3 (5 587.8, 8 430.1)	296	4 017.3 (3 430.7, 4 704.1)	284	3 690.6 (3 082.2, 4 419.0)
	1 month	105	23 641.3 (20 473.1, 27 299.8)	296	16 323.3 (14 686.5, 18 142.6)	286	16 250.1 (14 499.2, 18 212.4)

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

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4-5).

Comirnaty

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

Efficacy in participants 16 years of age and older – after 2 doses

In the Phase 2/3 portion of Study 2, based on data accrued through 14 November 2020, approximately 44 000 participants were randomised equally and were to receive 2 doses of the initially approved COVID-19 mRNA Vaccine or placebo. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. The majority (93.1%) of vaccine recipients received the second dose 19 days to 23 days after Dose 1. Participants are planned to be followed for up to 24 months after Dose 2, for assessments of safety and efficacy against COVID-19. In the clinical study, participants were required to observe a minimum interval of 14 days before and after administration of an influenza vaccine in order to receive either placebo or COVID-19 mRNA Vaccine. In the clinical study, participants were required to observe a minimum interval of 60 days before or after receipt of blood/plasma products or immunoglobulins within through conclusion of the study in order to receive either placebo or COVID-19 mRNA Vaccine.

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

At the time of the primary efficacy analysis, participants had been followed for symptomatic COVID-19 for in total 2 214 person-years for the COVID-19 mRNA Vaccine and in total 2 222 person-years in the placebo group.

There were no meaningful clinical differences in overall vaccine efficacy in participants who were at risk of severe COVID-19 including those with 1 or more comorbidities that increase the risk of severe COVID-19 (e.g. asthma, body mass index (BMI) ≥ 30 kg/m², chronic pulmonary disease, diabetes mellitus, hypertension).

The vaccine efficacy information is presented in Table 5.

Table 5. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of infection prior to 7 days after Dose 2 – evaluable efficacy (7 days) population

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 n^{1b} Surveillance time^c (n^{2d})	Placebo N^a = 18 325 Cases n^{1b} Surveillance time^c (n^{2d})	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.

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

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

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

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

The updated vaccine efficacy information is presented in Table 6.

Table 6. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of prior SARS-CoV-2 infection* prior to 7 days after Dose 2 – evaluable efficacy (7 days) population during the placebo-controlled follow-up period

Subgroup	COVID-19 mRNA Vaccine 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.

- N = Number of participants in the specified group.
- n1 = Number of participants meeting the endpoint definition.
- 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.
- n2 = Number of participants at risk for the endpoint.
- Two-sided 95% confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
- Included confirmed cases in participants 12 to 15 years of age: 0 in the COVID-19 mRNA Vaccine group; 16 in the placebo group.

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

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

Efficacy against severe COVID-19

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

As of 13 March 2021, vaccine efficacy against severe COVID-19 is presented only for participants with or without prior SARS-CoV-2 infection (Table 7) as the COVID-19 case counts in participants without prior SARS-CoV-2 infection were the same as those in participants with or without prior SARS-CoV-2 infection in both the COVID-19 mRNA Vaccine and placebo groups.

Table 7. Vaccine efficacy – First severe COVID-19 occurrence in participants with or without prior SARS-CoV-2 infection based on the Food and Drug Administration (FDA)* after Dose 1 or from 7 days after Dose 2 in the placebo-controlled follow-up

	COVID-19 mRNA Vaccine 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 $\leq 93\%$ on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen < 300 mm Hg);
 - Respiratory failure [defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
 - Evidence of shock (systolic blood pressure < 90 mm Hg, diastolic blood pressure < 60 mm Hg, or requiring vasopressors);
 - Significant acute renal, hepatic, or neurologic dysfunction;
 - Admission to an Intensive Care Unit;
 - Death.
- a. n1 = Number of participants meeting the endpoint definition.
 - b. n2 = Number of participants at risk for the endpoint.
 - c. Two-side confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
 - d. Efficacy assessed based on the Dose 1 all available efficacy (modified intention-to-treat) population that included all randomised participants who received at least 1 dose of study intervention.
 - e. Total surveillance time in 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 8. No cases of COVID-19 were observed in either the vaccine group or the placebo group in participants with evidence of prior SARS-CoV-2 infection.

Table 8. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2: Without evidence of infection prior to 7 days after Dose 2 – Phase 2/3 – Children 5 to 11 years of age evaluable efficacy population

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 prespecified immunobridging criteria for both the geometric mean ratio (GMR) and the seroresponse difference with seroresponse defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from baseline (before Dose 1).

The GMR of the SARS-CoV-2 NT50 1 month after Dose 2 in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) to that of young adults 16 to 25 years of age was 1.04 (2-sided 95% CI: 0.93, 1.18). Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, 99.2% of children 5 to 11 years of age and 99.2% of participants 16 to 25 years of age had a seroresponse at 1 month after Dose 2. The difference in proportions of participants who had seroresponse between the 2 age groups (children – young adult) was 0.0% (2-sided 95% CI: -2.0%, 2.2%). This information is presented in Table 9.

Table 9. Summary of geometric mean ratio for 50% neutralising titre and difference in percentages of participants with seroresponse – comparison of children 5 to 11 years of age (Study 3) to participants 16 to 25 years of age (Study 2) – participants without evidence of infection up to 1 month after Dose 2 – immunobridging subset – Phase 2/3 – evaluable immunogenicity population

		COVID-19 mRNA Vaccine		5 to 11 years/ 16 to 25 years	
		10 mcg/dose 5 to 11 years N ^a =264	30 mcg/dose 16 to 25 years N ^a =253		
	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% neutralizing 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 ⁱ)	Met immunobridging objective ^k (Y/N)
Seroresponse rate (%) for 50% neutralizing 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 postvaccination assay result $\geq 4 \times$ LLOQ is considered a seroresponse.

- N = Number of participants with valid and determinate assay results before vaccination and at 1 month after Dose 2. These values are also the denominators used in the percentage calculations for seroresponse rates.
- Protocol-specified timing for blood sample collection.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (5 to 11 years of age minus 16 to 25 years of age) and the corresponding CI (based on the Student t distribution).
- Immunobridging based on GMT is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥ 0.8 .
- SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralisation is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralised.
- n = Number of participants with seroresponse based on NT50 1 month after Dose 2.
- Exact 2-sided CI based on the Clopper and Pearson method.
- Difference in proportions, expressed as a percentage (5 to 11 years of age minus 16 to 25 years of age).
- 2-Sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
- Immunobridging based on seroresponse rate is declared if the lower bound of the 2-sided 95% CI for the seroresponse difference is greater than -10.0%.

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

A booster dose of Comirnaty was given to 401 randomly selected participants in Study 3. Effectiveness of a booster dose in ages 5 to 11 is inferred by immunogenicity. The immunogenicity of this was assessed through NT50 against the reference strain of SARS-CoV-2 (USA_WA1/2020). Analyses of NT50 1 month after the booster dose compared to before the booster dose demonstrated a substantial increase in GMTs in individuals 5 through 11 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the dose 2 and the booster dose. This analysis is summarized in Table 10.

Table 10. Summary of geometric mean titres – NT50 – participants without evidence of infection – phase 2/3 – immunogenicity set – 5 through 11 years of age – evaluable immunogenicity population

Assay	Sampling time point ^a		1 month after booster dose/ 1 month after dose 2
	1 month after booster dose (n ^b =67)	1 month after dose 2 (n ^b =96)	
	GMT ^c (95% CI ^c)	GMT ^c (95% CI ^c)	GMR ^d (95% CI ^d)
SARS-CoV-2 neutralization 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% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome corona virus 2.

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ 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).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Comirnaty in 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 neutralizing antibody responses were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in foetuses and offspring. There were no vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development. No Comirnaty data are available on vaccine placental transfer or excretion in milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened vial

Frozen vial

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

The vaccine will be received frozen at -90 °C to -60 °C. Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

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 or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Multidose vials

When stored frozen at -90 °C to -60 °C, 10-vial packs of multidose vials of the vaccine can be thawed at 2 °C to 8 °C for 6 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed vial

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

- Upon moving the vaccine to 2 °C to 8 °C storage, the updated expiry date must be written on the outer carton and the vaccine should be used or discarded by the updated expiry date. The original expiry date should be crossed out.
- If the vaccine is received at 2 °C to 8 °C it should be stored at 2 °C to 8 °C. The expiry date on the outer carton should have been updated to reflect the refrigerated expiry date and the original expiry date should have been crossed out.

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

Thawed vials can be handled in room light conditions.

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

Handling of temperature excursions during refrigerated storage

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

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

Opened vial

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

6.4 Special precautions for storage

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

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

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

For storage conditions after thawing and first opening, see section 6.3.

6.5 Nature and contents of container

Comirnaty Original/Omicron BA.4-5 dispersion is supplied in a 2 mL clear vial (type I glass) with a stopper (synthetic bromobutyl rubber) and a blue flip-off plastic cap with aluminium seal.

One single dose vial contains 1 dose of 0.3 mL, see sections 4.2 and 6.6.

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

Single dose vial pack size: 10 vials.

Multidose vial pack size: 10 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Handling instructions prior to use

Comirnaty Original/Omicron BA.4-5 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- **Verify** that the vial has a **blue plastic cap** and the product **name is Comirnaty Original/Omicron BA.4-5 (5/5 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 Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw. Ensure vials are completely thawed prior to use.
 - 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).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Preparation of 0.3 mL doses

- Gently mix by inverting vials 10 times prior to use. Do not shake.
- Prior to mixing, the thawed dispersion may contain white to off-white opaque amorphous particles.
- After mixing, the vaccine should present as a clear to slightly opalescent dispersion with no particulates visible. Do not use the vaccine if particulates or discolouration are present.

- 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 Original/Omicron BA.4-5 for children aged 5 to 11 years.
- 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 vial. Discard any unused vaccine 12 hours after first puncture.

Disposal

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

Single dose vials

EU/1/20/1528/015

Multidose vials

EU/1/20/1528/016

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 December 2020

Date of latest renewal: 10 October 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

▼ 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 Original/Omicron BA.4-5 (1.5/1.5 micrograms)/dose concentrate for dispersion for injection
COVID-19 mRNA Vaccine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

One vial (0.4 mL) contains 10 doses of 0.2 mL after dilution, see sections 4.2 and 6.6.

One dose (0.2 mL) contains 1.5 micrograms of tozinameran, and 1.5 micrograms of famtozinameran, a COVID-19 mRNA Vaccine (nucleoside modified, embedded in lipid nanoparticles).

Tozinameran 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 (Original). Famtozinameran 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 BA.4-5).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Comirnaty Original/Omicron BA.4-5 (1.5/1.5 micrograms)/dose concentrate for dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in infants and children aged 6 months to 4 years.

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 Original/Omicron BA.4-5 (1.5/1.5 micrograms)/dose is administered intramuscularly after dilution as a primary course of 3 doses (0.2 mL each). It is recommended to administer the second dose 3 weeks after the first dose followed by a third dose administered at least 8 weeks after the second dose (see sections 4.4 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 or 1.5/1.5 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 Original/Omicron BA.4-5 (1.5/1.5 micrograms/dose) is administered intramuscularly after dilution as a single dose of 0.2 mL for infants and children 6 months to 4 years of age.

For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty Original/Omicron BA.4-5 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Severely immunocompromised aged 6 months to 4 years

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

Interchangeability

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

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

Paediatric population

There are paediatric formulations available for children 5 to 11 years of age. For details, please refer to the 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 Original/Omicron BA.4-5 (1.5/1.5 micrograms)/dose concentrate for dispersion for injection should be administered intramuscularly after dilution (see section 6.6).

After dilution, vials of Comirnaty Original/Omicron BA.4-5 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.

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

The efficacy and safety of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of Comirnaty Original/Omicron BA.4-5 may be lower in immunocompromised individuals.

Duration of protection

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

Limitations of vaccine effectiveness

As with any vaccine, vaccination with Comirnaty Original/Omicron BA.4-5 may not protect all vaccine recipients. Individuals may not be fully protected until 7 days after their vaccination.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concomitant administration of Comirnaty Original/Omicron BA.4-5 with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation

Comirnaty Original/Omicron BA.4-5 (1.5/1.5 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 Original/Omicron BA.4-5 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 a dose of Comirnaty Original/Omicron BA.4-5 is inferred from safety data from Comirnaty and Omicron adapted vaccines.

Comirnaty

Infants 6 to 23 months of age – after 3 doses

In an analysis of Study 3 (Phase 2/3), 1 776 infants (1 178 initially approved Comirnaty 3 mcg and 598 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 29 April 2022, 570 infants 6 to 23 months of age who received a 3-dose primary course (386 Comirnaty 3 mcg and 184 placebo) have been followed for a median of 1.3 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), 2 750 children (1 835 Comirnaty 3 mcg and 915 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 29 April 2022, 886 children 2 to 4 years of age who received a 3-dose primary course

(606 Comirnaty 3 mcg and 280 placebo) have been followed a median of 1.4 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 Comirnaty 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 \geq 4 months after the second dose in the placebo-controlled blinded follow-up period. The safety evaluation in Study 3 is ongoing.

The overall safety profile of Comirnaty in participants 5 to 11 years of age was similar to that seen in participants 16 years of age and older. The most frequent adverse reactions in children 5 to 11 years of age that received 2 doses were injection site pain (> 80%), fatigue (> 50%), headache (> 30%), injection site redness and swelling (\geq 20%), myalgia, chills and diarrhoea (> 10%).

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

In a subset from Study 3, a total of 401 children 5 to 11 years of age received a booster dose of Comirnaty 10 mcg at least 5 months (range of 5 to 9 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 22 March 2022 (median follow-up time of 1.3 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 were injection site pain (> 70%), fatigue (> 40%), headache (> 30%), 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 \geq 4 months after the second dose of Comirnaty.

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

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

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

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

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

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

In a subset from Study 6 (Phase 3), 113 participants 5 to 11 years of age who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (5/5 mcg) 2.6 to

8.5 months after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 had a median follow-up time of at least 1.6 months.

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

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

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

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

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

Adverse reactions observed during clinical studies are listed below according to the following frequency categories: Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1\ 000$ to $< 1/100$), Rare ($\geq 1/10\ 000$ to $< 1/1\ 000$), Very rare ($< 1/10\ 000$), Not known (cannot be estimated from the available data).

Table 1. Adverse reactions from Comirnaty 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
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

System Organ Class	Frequency	Adverse reactions
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

- In participants 5 years of age and older, a higher frequency of lymphadenopathy was reported after a booster ($\leq 2.8\%$) dose than after primary ($\leq 0.9\%$) doses of the vaccine.
- The frequency category for angioedema was rare.
- Through the clinical trial safety follow-up period to 14 November 2020, acute peripheral facial paralysis (or palsy) was reported by four participants in the COVID-19 mRNA Vaccine group. Onset was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.
- Adverse reaction determined post-authorization.
- Refers to vaccinated arm.
- A higher frequency of pyrexia was observed after the second dose compared to the first dose.
- Facial swelling in vaccine recipients with a history of injection of dermatological fillers has been reported in the post-marketing phase.
- Injection site redness occurred at a higher frequency (very common) in participants 6 months to 11 years of age.
- The frequency category for rash was common in participants 6 to 23 months of age.
- The frequency category for decreased appetite was very common in participants 6 to 23 months of age.
- Irritability, injection site tenderness, and drowsiness pertain to participants 6 to 23 months of age.
- Most cases appeared to be non-serious and temporary in nature.

Description of selected adverse reactions

Myocarditis and pericarditis

The increased risk of myocarditis after vaccination with Comirnaty is highest in younger males (see section 4.4).

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 listed in Appendix V](#) and include batch/Lot number if available.

4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vaccines, viral vaccines, ATC code: J07BN01

Mechanism of action

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

Efficacy

Omicron-adapted Comirnaty

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

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

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

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

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

SARS-CoV-2 neutralization assay	Age group	Sampling time point ^a	Vaccine group (as assigned/randomized)			
			Study 6 Comirnaty Original/Omicron BA.4-5 1.5/1.5 mcg Dose 4 and 1 month after Dose 4		Study 3 Comirnaty 3 mcg Dose 3 and 1 month after Dose 3	
			n ^b	GMT ^c (95% CI ^c)	n ^b	GMT ^c (95% CI ^c)
Omicron BA.4-5 - NT50 (titre) ^d	6 months through 4 years	Pre-vaccination	54	192.5 (120.4, 307.8)	54	70.5 (51.1, 97.2)
		1 month	58	1 695.2 (1 151.8, 2 494.9)	54	607.9 (431.1, 857.2)
Reference strain - NT50 (titre) ^d	6 months through 4 years	Pre-vaccination	57	2 678.1 (1 913.0, 3 749.2)	53	776.8 (536.4, 1 125.0)
		1 month	58	9 733.0 (7 708.2, 12 289.6)	53	9 057.3 (7 223.4, 11 356.8)

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

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).

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

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

The immune response 1 month after a booster dose (fourth dose), Comirnaty Original/Omicron BA.4-5 elicited generally similar Omicron BA.4/BA.5-specific neutralizing titres compared with the titres in the comparator group who received 3 doses of Comirnaty. Comirnaty Original/Omicron BA.4-5 also elicited similar reference strain-specific titres compared with the titres in the comparator group.

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

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

SARS-CoV-2 neutralization assay	Sampling time point ^a	Vaccine group (as assigned/randomized)				
		Study 6 Comirnaty (Original/Omicron BA.4/BA.5) 10 mcg Dose 4 and 1 month after Dose 4		Study 3 Comirnaty 10 mcg Dose 3 and 1 month after Dose 3		Study 6 Comirnaty (Original/Omicron BA.4/BA.5)/Comirnaty 10 mcg
		n ^b	GMT ^c (95% CI ^e)	n ^b	GMT ^c (95% CI ^e)	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% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.

- d. GMRs and 2-sided CIs were calculated by exponentiating the difference of LS Means for the assay and the corresponding CIs based on an analysis of log-transformed assay results using a linear regression model with baseline log-transformed neutralizing titers, postbaseline infection status, and vaccine group as covariates.
- e. SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).

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

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

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

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

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

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

SARS-CoV-2 GMTs (NT50) at 1 month after vaccination course								
SARS-CoV-2 neutralization assay	Study 5 Comirnaty Original/Omicron BA.4-5				Subset of Study 4 Comirnaty		Age group comparison	Vaccine group comparison
	18 through 55 years of age		56 years of age and older		56 years of age and older		Comirnaty Original/Omicron BA.4-5 18 through 55 years of age/≥56 years of age	≥56 years of age Comirnaty Original/Omicron BA.4-5 /Comirnaty
	n ^a	GMT ^c (95% CI ^c)	n ^a	GMT ^b (95% CI ^b)	n ^a	GMT ^b (95% CI ^b)	GMR ^c (95% CI ^c)	GMR ^c (95% CI ^c)
	Omicron BA.4-5 - NT50 (titre) ^d	297	4 455.9 (3 851.7, 5 154.8)	284	4 158.1 (3 554.8, 4 863.8)	282	938.9 (802.3, 1 098.8)	0.98 (0.83, 1.16) ^e
Reference Strain – NT50 (titre) ^d	-	-	286	16 250.1 (14 499.2, 18 212.4)	289	10 415.5 (9 366.7, 11 581.8)	-	1.38 (1.22, 1.56) ^g

Difference in percentages of participants with seroresponse at 1 month after vaccination course								
	Comirnaty Original/Omicron BA.4-5				Subset of Study 4 Comirnaty		Age group comparison	Vaccine group comparison ≥ 56 years of age
	18 through 55 years of age		56 years of age and older		56 years of age and older		Comirnaty Original/Omicron BA.4-5 18 through 55 years of age/ ≥ 56	Comirnaty Original/Omicron BA.4-5 /Comirnaty
SARS-CoV-2 neutralization assay	N ^h	n ⁱ (%) (95% CI ^k)	N ^h	n ⁱ (%) (95% CI ^k)	N ^h	n ⁱ (%) (95% CI ^l)	Difference ^k (95% CI ^l)	Difference ^k (95% CI ^l)
Omicron BA.4-5 - NT50 (titre) ^d	294	180 (61.2) (55.4, 66.8)	282	188 (66.7) (60.8, 72.1)	273	127 (46.5) (40.5, 52.6)	-3.03 (-9.68, 3.63) ^m	26.77 (19.59, 33.95) ⁿ

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

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

- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the difference of LS means and corresponding CIs based on analysis of logarithmically transformed neutralizing titres using a linear regression model with terms of baseline neutralizing titre (log scale) and vaccine group or age group.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).
- Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67.
- Superiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 1.
- Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥ 0.8 .
- N = Number of participants with valid and determinate assay results for the specified assay at both the prevaccination time point and the given sampling time point. This value is the denominator for the percentage calculation.
- n = Number of participants with seroresponse for the given assay at the given sampling time point.
- Exact 2-sided CI, based on the Clopper and Pearson method.
- Difference in proportions, expressed as a percentage.
- 2-sided CI based on the Miettinen and Nurminen method stratified by baseline neutralizing titre category (< median, \geq median) for the difference in proportions. The median of baseline neutralizing titres was calculated based on the pooled data in 2 comparator groups.
- Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is $> -10\%$.
- Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is $> -5\%$.

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

SARS-CoV-2 neutralization assay	Sampling time point ^a	Comirnaty Original/Omicron BA.4-5					
		12 through 17 years of age		18 through 55 years of age		56 years of age and older	
		n ^b	GMT ^c (95% CI ^c)	n ^b	GMT ^c (95% CI ^c)	n ^b	GMT ^c (95% CI ^c)
Omicron BA.4-5 - NT50 (titre) ^d	Pre-vaccination	104	1 105.8 (835.1, 1 464.3)	294	569.6 (471.4, 688.2)	284	458.2 (365.2, 574.8)
	1 month	105	8 212.8 (6 807.3, 9 908.7)	297	4 455.9 (3 851.7, 5 154.8)	284	4 158.1 (3 554.8, 4 863.8)
Reference strain - NT50 (titre) ^d	Pre-vaccination	105	6 863.3 (5 587.8, 8 430.1)	296	4 017.3 (3 430.7, 4 704.1)	284	3 690.6 (3 082.2, 4 419.0)
	1 month	105	23 641.3 (20 473.1, 27 299.8)	296	16 323.3 (14 686.5, 18 142.6)	286	16 250.1 (14 499.2, 18 212.4)

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

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4-5).

Comirnaty

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

Efficacy in participants 16 years of age and older – after 2 doses

In the Phase 2/3 portion of Study 2, based on data accrued through 14 November 2020, approximately 44 000 participants were randomised equally and were to receive 2 doses of the initially approved COVID-19 mRNA Vaccine or placebo. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. The majority (93.1%) of vaccine recipients received the second dose 19 days to 23 days after Dose 1. Participants are planned to be followed for up to 24 months after Dose 2, for assessments of safety and efficacy against COVID-19. In the clinical study, participants were required to observe a minimum interval of 14 days before and after administration of an influenza vaccine in order to receive either placebo or COVID-19 mRNA Vaccine. In the clinical study, participants were required to observe a minimum interval of 60 days before or after receipt of blood/plasma products or immunoglobulins within through conclusion of the study in order to receive either placebo or COVID-19 mRNA Vaccine.

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

mRNA Vaccine group and 68 in the placebo group) and 1 616 participants 75 years of age and older (804 in the COVID-19 mRNA Vaccine group and 812 in the placebo group).

At the time of the primary efficacy analysis, participants had been followed for symptomatic COVID-19 for in total 2 214 person-years for the COVID-19 mRNA Vaccine and in total 2 222 person-years in the placebo group.

There were no meaningful clinical differences in overall vaccine efficacy in participants who were at risk of severe COVID-19 including those with 1 or more comorbidities that increase the risk of severe COVID-19 (e.g. asthma, body mass index (BMI) ≥ 30 kg/m², chronic pulmonary disease, diabetes mellitus, hypertension).

The vaccine efficacy information is presented in Table 6.

Table 6. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of infection prior to 7 days after Dose 2 – evaluable efficacy (7 days) population

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 n^{1b} Surveillance time^c (n^{2d})	Placebo N^a = 18 325 Cases n^{1b} Surveillance time^c (n^{2d})	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 7.

Table 7. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of prior SARS-CoV-2 infection* prior to 7 days after Dose 2 – evaluable efficacy (7 days) population during the placebo-controlled follow-up period

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.

- N = Number of participants in the specified group.
- n1 = Number of participants meeting the endpoint definition.
- 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.
- n2 = Number of participants at risk for the endpoint.
- Two-sided 95% confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
- Included confirmed cases in participants 12 to 15 years of age: 0 in the COVID-19 mRNA Vaccine group; 16 in the placebo group.

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

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

Efficacy against severe COVID-19

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

As of 13 March 2021, vaccine efficacy against severe COVID-19 is presented only for participants with or without prior SARS-CoV-2 infection (Table 8) as the COVID-19 case counts in participants without prior SARS-CoV-2 infection were the same as those in participants with or without prior SARS-CoV-2 infection in both the COVID-19 mRNA Vaccine and placebo groups.

Table 8. Vaccine efficacy – First severe COVID-19 occurrence in participants with or without prior SARS-CoV-2 infection based on the Food and Drug Administration (FDA)* after Dose 1 or from 7 days after Dose 2 in the placebo-controlled follow-up

	COVID-19 mRNA Vaccine Cases n1 ^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 $\leq 93\%$ on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen < 300 mm Hg);
- Respiratory failure [defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
- Evidence of shock (systolic blood pressure < 90 mm Hg, diastolic blood pressure < 60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an Intensive Care Unit;
- Death.

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

b. n2 = Number of participants at risk for the endpoint.

c. Two-side confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.

d. Efficacy assessed based on the Dose 1 all a 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 9. No cases of COVID-19 were observed in either the vaccine group or the placebo group in participants with evidence of prior SARS-CoV-2 infection.

Table 9. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2: Without evidence of infection prior to 7 days after Dose 2 – Phase 2/3 – Children 5 to 11 years of age evaluable efficacy population

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 n^{1b} Surveillance time^c (n^{2d})	Placebo N^a=663 Cases n^{1b} Surveillance time^c (n^{2d})	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 prespecified immunobridging criteria for both the geometric mean ratio (GMR) and the seroresponse difference with seroresponse defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from baseline (before Dose 1).

The GMR of the SARS-CoV-2 NT50 1 month after Dose 2 in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) to that of young adults 16 to 25 years of age was 1.04 (2-sided 95% CI: 0.93, 1.18). Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, 99.2% of children 5 to 11 years of age and 99.2% of participants 16 to 25 years of age had a seroresponse at 1 month after Dose 2. The difference in proportions of participants who had seroresponse between the 2 age groups (children – young adult) was 0.0% (2-sided 95% CI: -2.0%, 2.2%). This information is presented in Table 10.

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

		COVID-19 mRNA Vaccine		5 to 11 years/ 16 to 25 years	
		10 mcg/dose 5 to 11 years N ^a =264	30 mcg/dose 16 to 25 years N ^a =253		
	Time point ^b	GMT ^c (95% CI ^e)	GMT ^c (95% CI ^e)	GMR ^d (95% CI ^d)	Met immunobridging objective ^e (Y/N)
Geometric mean 50% neutralizing 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% neutralizing 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 postvaccination assay result $\geq 4 \times$ LLOQ is considered a seroresponse.

- N = Number of participants with valid and determinate assay results before vaccination and at 1 month after Dose 2. These values are also the denominators used in the percentage calculations for seroresponse rates.
- Protocol-specified timing for blood sample collection.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (5 to 11 years of age minus 16 to 25 years of age) and the corresponding CI (based on the Student t distribution).
- Immunobridging based on GMT is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥ 0.8 .
- SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralisation is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralised.
- n = Number of participants with seroresponse based on NT50 1 month after Dose 2.
- Exact 2-sided CI based on the Clopper and Pearson method.
- Difference in proportions, expressed as a percentage (5 to 11 years of age minus 16 to 25 years of age).
- 2-Sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
- Immunobridging based on seroresponse rate is declared if the lower bound of the 2-sided 95% CI for the seroresponse difference is greater than -10.0%.

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

A booster dose of Comirnaty was given to 401 randomly selected participants in Study 3. Effectiveness of a booster dose in ages 5 to 11 is inferred by immunogenicity. The immunogenicity of this was assessed through NT50 against the reference strain of SARS-CoV-2 (USA_WA1/2020). Analyses of NT50 1 month after the booster dose compared to before the booster dose demonstrated a substantial increase in GMTs in individuals 5 through 11 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the dose 2 and the booster dose. This analysis is summarized in Table 11.

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

Assay	Sampling time point ^a		
	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 neutralization 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% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

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

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

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

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

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

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 through 4 years ^e	13 0.124 (794)	21 0.054 (351)	73.2 (43.8, 87.6)
2 through 4 years	9 0.081 (498)	13 0.033 (204)	71.8 (28.6, 89.4)
6 months through 23 months	4 0.042 (296)	8 0.020 (147)	75.8 (9.7, 94.7)

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

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

- N = number of participants in the specified group.
- n1 = Number of participants meeting the endpoint definition.
- 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.
- n2 = Number of participants at risk for the endpoint.
- Two-sided 95% confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.

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

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

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

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

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

prespecified immunobridging criteria were met for both the GMR and the seroresponse difference for both age groups (Table 13).

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

SARS-CoV-2 GMTs (NT50) at 1 month after vaccination course							
SARS-CoV-2 neutralization 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 neutralization 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
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 postvaccination assay result $\geq 4 \times$ LLOQ is considered a seroresponse.

- N = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point for GMTs and number of participants with valid and determinate assay results for the specified assay at both baseline and the given dose/sampling time point for seroresponse rates.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.

- 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 neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralised.
- f. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.
- g. Exact 2-sided CI based on the Clopper and Pearson method.
- h. Difference in proportions, expressed as a percentage (younger age group minus 16 to 25 years of age).
- i. 2-sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
- j. For each younger age group (2 to 4 years, 6 to 23 months), immunobridging based on seroresponse rate is declared if the lower bound of the 2-sided 95% CI for the difference in proportions is greater than -10.0% provided that the immunobridging criteria based on GMR were met.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Comirnaty in 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 neutralizing antibody responses were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in foetuses and offspring. There were no vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development. No Comirnaty data are available on vaccine placental transfer or excretion in milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

((4-hydroxybutyl)azanediy)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

Unopened vial

Frozen vial

2 years when stored at -90 °C to -60 °C.

The vaccine will be received frozen at -90 °C to -60 °C. Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

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

Thawed vial

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

- Upon moving the vaccine to 2 °C to 8 °C storage, the updated expiry date must be written on the outer carton and the vaccine should be used or discarded by the updated expiry date. The original expiry date should be crossed out.
- If the vaccine is received at 2 °C to 8 °C it should be stored at 2 °C to 8 °C. The expiry date on the outer carton should have been updated to reflect the refrigerated expiry date and the original expiry date should have been crossed out.

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

Thawed vials can be handled in room light conditions.

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

Handling of temperature excursions during refrigerated storage

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

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

Diluted medicinal product

Chemical and physical in-use stability has been demonstrated for 12 hours at 2 °C to 30 °C, after dilution with sodium chloride 9 mg/mL (0.9%) solution for injection, which includes up to 6 hours transportation time. From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

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

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

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

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

6.5 Nature and contents of container

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

6.6 Special precautions for disposal and other handling

Handling instructions prior to use

Comirnaty Omicron/Original BA.4-5 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- **Verify** that the vial has a **maroon plastic cap** and the product **name is Comirnaty Original/Omicron BA.4-5 (1.5/1.5 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, please make reference to the Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 10-vial pack may take 2 hours to thaw. Ensure vials are completely thawed prior to use.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Dilution

- 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 **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 2.2 mL air into the empty diluent syringe.

- Gently invert the diluted dispersion 10 times. Do not shake.
- The diluted vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discolouration are present.
- The diluted vials should be marked with the appropriate **discard date and time**.
- **After dilution**, store at 2 °C to 30 °C and use within **12 hours**.
- Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.

Preparation of 0.2 mL doses

- 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 Original/Omicron BA.4-5 for infants and children aged 6 months to 4 years.
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 12 hours after dilution.

Disposal

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

7. MARKETING AUTHORISATION HOLDER

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Germany
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8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1528/017

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 December 2020

Date of latest renewal: 10 October 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

▼ 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 Omicron XBB.1.5 30 micrograms/dose dispersion for injection
COVID-19 mRNA Vaccine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

This is a single dose or a multidose vial with a grey cap. Do not dilute prior to use.

One single dose vial contains 1 dose of 0.3 mL, see sections 4.2 and 6.6.

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

One dose (0.3 mL) contains 30 micrograms of raxtozinameran, a COVID-19 mRNA Vaccine (nucleoside modified, embedded in lipid nanoparticles).

Raxtozinameran is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 (Omicron XBB.1.5).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersion for injection.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Comirnaty Omicron XBB.1.5 30 micrograms/dose dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 12 years of age and older.

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

4.2 Posology and method of administration

Posology

Individuals 12 years of age and older

Comirnaty Omicron XBB.1.5 30 micrograms/dose is administered intramuscularly as a single dose of 0.3 mL for individuals 12 years of age and older regardless of prior COVID-19 vaccination status (see sections 4.4 and 5.1).

For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty Omicron XBB.1.5 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Severely immunocompromised aged 12 years and older

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

Paediatric population

There are paediatric formulations available for infants aged 6 months and above and children below 12 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.

Elderly population

No dose adjustment is required in elderly individuals ≥ 65 years of age.

Method of administration

Comirnaty Omicron XBB.1.5 30 micrograms/dose dispersion for injection should be administered intramuscularly (see section 6.6). Do not dilute prior to use.

The preferred site is the deltoid muscle of the upper arm.

Do not inject the vaccine intravascularly, subcutaneously or intradermally.

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

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

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

Single dose vials

Single dose vials of Comirnaty Omicron XBB.1.5 contain 1 dose of 0.3 mL of vaccine.

- Withdraw a single 0.3 mL dose of Comirnaty Omicron XBB.1.5.
- Discard vial and any excess volume.
- Do not pool excess vaccine from multiple vials.

Multidose vials

Multidose vials of Comirnaty Omicron XBB.1.5 contain 6 doses of 0.3 mL of vaccine. In order to extract 6 doses from a single vial, low dead-volume syringes and/or needles should be used. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial. Irrespective of the type of syringe and needle:

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Traceability

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

General recommendations

Hypersensitivity and anaphylaxis

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

Close observation for at least 15 minutes is recommended following vaccination. No further dose of the vaccine should be given to those who have experienced anaphylaxis after a prior dose of Comirnaty.

Myocarditis and pericarditis

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

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

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

Anxiety-related reactions

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

Concurrent illness

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

Thrombocytopenia and coagulation disorders

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

Immunocompromised individuals

The efficacy and safety of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of Comirnaty Omicron XBB.1.5 may be lower in immunocompromised individuals.

Duration of protection

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

Limitations of vaccine effectiveness

As with any vaccine, vaccination with Comirnaty Omicron XBB.1.5 may not protect all vaccine recipients. Individuals may not be fully protected until 7 days after their vaccination.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concomitant administration of Comirnaty Omicron XBB.1.5 with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

No data are available yet regarding the use of Comirnaty Omicron XBB.1.5 during pregnancy.

However, a large amount of observational data from pregnant women vaccinated with the initially approved Comirnaty vaccine during the second and third trimester have not shown an increase in adverse pregnancy outcomes. While data on pregnancy outcomes following vaccination during the first trimester are presently limited, no increased risk for miscarriage has been seen. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development (see section 5.3). Based on data available with other vaccine variants, Comirnaty Omicron XBB.1.5 can be used during pregnancy.

Breast-feeding

No data are available yet regarding the use of Comirnaty Omicron XBB.1.5 during breast-feeding.

However, no effects on the breastfed newborn/infant are anticipated since the systemic exposure of breast-feeding woman to the vaccine is negligible. Observational data from women who were breast-feeding after vaccination with the initially approved Comirnaty vaccine have not shown a risk for adverse effects in breastfed newborns/infants. Comirnaty Omicron XBB.1.5 can be used during breast-feeding.

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of safety profile

The safety of Comirnaty Omicron XBB.1.5 is inferred from safety data of the prior Comirnaty vaccines.

Comirnaty 30 mcg

Participants 16 years of age and older – after 2 doses

In Study 2, a total of 22 026 participants 16 years of age or older received at least 1 dose of the initially approved Comirnaty vaccine and a total of 22 021 participants 16 years of age or older received placebo (including 138 and 145 adolescents 16 and 17 years of age in the vaccine and placebo groups, respectively). A total of 20 519 participants 16 years of age or older received 2 doses of Comirnaty.

At the time of the analysis of Study 2 with a data cut-off of 13 March 2021 for the placebo-controlled blinded follow-up period up to the participants' unblinding dates, a total of 25 651 (58.2%) participants (13 031 Comirnaty and 12 620 placebo) 16 years of age and older were followed up for ≥ 4 months after the second dose. This included a total of 15 111 (7 704 Comirnaty and 7 407 placebo) participants 16 to 55 years of age and a total of 10 540 (5 327 Comirnaty and 5 213 placebo) participants 56 years of age and older.

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

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

Adolescents 12 to 15 years of age – after 2 doses

In an analysis of long-term safety follow-up in Study 2, 2 260 adolescents (1 131 Comirnaty and 1 129 placebo) were 12 to 15 years of age. Of these, 1 559 adolescents (786 Comirnaty and 773 placebo) have been followed for ≥ 4 months after the second dose of Comirnaty.

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

Participants 12 years of age and older – after booster dose

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 (see section 5.1).

Omicron-adapted Comirnaty

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

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

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

Tabulated list of adverse reactions from clinical studies of Comirnaty and Comirnaty Original/Omicron BA.4-5 and post-authorisation experience of Comirnaty in individuals 12 years of age and older

Adverse reactions observed during clinical studies are listed below according to the following frequency categories: Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1\ 000$ to $< 1/100$), Rare ($\geq 1/10\ 000$ to $< 1/1\ 000$), Very rare ($< 1/10\ 000$), Not known (cannot be estimated from the available data).

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

System Organ Class	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

System Organ Class	Frequency	Adverse reactions
Gastrointestinal disorders	Very common	Diarrhoea ^d
	Common	Nausea; vomiting ^d
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 ^h
General disorders and administration site conditions	Very common	Injection site pain; fatigue; chills; pyrexia ^f ; injection site swelling
	Common	Injection site redness
	Uncommon	Asthenia; malaise; injection site pruritus
	Not known	Extensive swelling of vaccinated limb ^d ; facial swelling ^g

- In participants 5 years of age and older, a higher frequency of lymphadenopathy was reported after a booster ($\leq 2.8\%$) dose than after primary ($\leq 0.9\%$) doses of the vaccine.
- The frequency category for urticaria and angioedema was rare.
- Through the clinical trial safety follow-up period to 14 November 2020, acute peripheral facial paralysis (or palsy) was reported by four participants in the COVID-19 mRNA Vaccine group. Onset was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.
- Adverse reaction determined post-authorization.
- Refers to vaccinated arm.
- A higher frequency of pyrexia was observed after the second dose compared to the first dose.
- Facial swelling in vaccine recipients with a history of injection of dermatological fillers has been reported in the post-marketing phase.
- Most cases appeared to be non-serious and temporary in nature.

Description of selected adverse reactions

Myocarditis and pericarditis

The increased risk of myocarditis after vaccination with Comirnaty is highest in younger males (see section 4.4).

Two large European pharmacoepidemiological studies have estimated the excess risk in younger males following the second dose of Comirnaty. One study showed that in a period of 7 days after the second dose there were about 0.265 (95% CI 0.255 - 0.275) extra cases of myocarditis in 12-29 year old males per 10 000 compared to unexposed persons. In another study, in a period of 28 days after the second dose there were 0.56 (95% CI 0.37 - 0.74) extra cases of myocarditis in 16-24 year old males per 10 000 compared to unexposed persons.

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via [the national reporting system listed in Appendix V](#) and include batch/Lot number if available.

4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vaccines, viral vaccines, ATC code: J07BN01

Mechanism of action

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

Efficacy

Omicron-adapted Comirnaty

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

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

Analyses of 50% neutralizing antibody titres (NT50) against Omicron BA.4-5 and against reference strain among participants 56 years of age and older who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 in Study 5 compared to a subset of participants from Study 4 who received a booster (fourth dose) of Comirnaty demonstrated superiority of Comirnaty Original/Omicron BA.4-5 to Comirnaty based on geometric mean ratio (GMR) and noninferiority based on difference in seroresponse rates with respect to anti-Omicron BA.4-5 response, and noninferiority of anti-reference strain immune response based on GMR (Table 2).

Analyses of NT50 against Omicron BA.4/BA.5 among participants 18 to 55 years of age compared to participants 56 years of age and older who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 in Study 5 demonstrated noninferiority of anti-Omicron BA.4-5 response among participants 18 to 55 years of age compared to participants 56 years of age and older for both GMR and difference in seroresponse rates (Table 2).

The study also assessed the level of NT50 of the anti-Omicron BA.4-5 SARS-CoV-2 and reference strains pre-vaccination and 1 month after vaccination in participants who received a booster (fourth dose) (Table 3).

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

SARS-CoV-2 GMTs (NT50) at 1 month after vaccination course								
SARS-CoV-2 neutralization assay	Study 5 Comirnaty Original/Omicron BA.4-5				Subset of Study 4 Comirnaty		Age group comparison	Vaccine group comparison
	18 through 55 years of age		56 years of age and older		56 years of age and older		Comirnaty Original/Omicron BA.4-5 18 through 55 years of age/≥ 56 years of age	≥ 56 years of age Comirnaty Original/Omicron BA.4-5 /Comirnaty
	n ^a	GMT ^c (95% CI ^c)	n ^a	GMT ^b (95% CI ^b)	n ^a	GMT ^b (95% CI ^b)	GMR ^c (95% CI ^c)	GMR ^c (95% CI ^c)
Omicron BA.4-5 - NT50 (titre) ^d	297	4 455.9 (3 851.7, 5 154.8)	284	4 158.1 (3 554.8, 4 863.8)	282	938.9 (802.3, 1 098.8)	0.98 (0.83, 1.16) ^e	2.91 (2.45, 3.44) ^f
Reference Strain – NT50 (titre) ^d	-	-	286	16 250.1 (14 499.2, 18 212.4)	289	10 415.5 (9 366.7, 11 581.8)	-	1.38 (1.22, 1.56) ^g
Difference in percentages of participants with seroresponse at 1 month after vaccination course								
SARS-CoV-2 neutralization assay	Comirnaty Original/Omicron BA.4-5				Subset of Study 4 Comirnaty		Age group comparison	Vaccine group comparison
	18 through 55 years of age		56 years of age and older		56 years of age and older		Comirnaty Original/Omicron BA.4-5 18 through 55 years of age/≥ 56	≥ 56 years of age Comirnaty Original/Omicron BA.4-5 /Comirnaty
	N ^h	n ⁱ (%) (95% CI ^k)	N ^h	n ⁱ (%) (95% CI ^k)	N ^h	n ⁱ (%) (95% CI ^j)	Difference ^k (95% CI ^l)	Difference ^k (95% CI ^l)
Omicron BA.4-5 - NT50 (titre) ^d	294	180 (61.2) (55.4, 66.8)	282	188 (66.7) (60.8, 72.1)	273	127 (46.5) (40.5, 52.6)	-3.03 (-9.68, 3.63) ^m	26.77 (19.59, 33.95) ⁿ

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

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

- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the difference of LS means and corresponding CIs based on analysis of logarithmically transformed neutralizing titres using a linear regression model with terms of baseline neutralizing titre (log scale) and vaccine group or age group.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).
- Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67.
- Superiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 1.
- Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥ 0.8.

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

Table 3. Geometric mean titres – Comirnaty Original/Omicron BA.4-5 subsets of Study 5 – prior to and 1 month after booster (fourth dose) – participants 12 years of age and older – with or without evidence of infection - evaluable immunogenicity population

SARS-CoV-2 neutralization assay	Sampling time point ^a	Comirnaty Original/Omicron BA.4-5					
		12 through 17 years of age		18 through 55 years of age		56 years of age and older	
		n ^b	GMT ^c (95% CI ^c)	n ^b	GMT ^c (95% CI ^c)	n ^b	GMT ^c (95% CI ^c)
Omicron BA.4-5 - NT50 (titre) ^d	Pre-vaccination	104	1 105.8 (835.1, 1 464.3)	294	569.6 (471.4, 688.2)	284	458.2 (365.2, 574.8)
	1 month	105	8 212.8 (6 807.3, 9 908.7)	297	4 455.9 (3 851.7, 5 154.8)	284	4 158.1 (3 554.8, 4 863.8)
Reference Strain – NT50 (titre) ^d	Pre-vaccination	105	6 863.3 (5 587.8, 8 430.1)	296	4 017.3 (3 430.7, 4 704.1)	284	3 690.6 (3 082.2, 4 419.0)
	1 month	105	23 641.3 (20 473.1, 27 299.8)	296	16 323.3 (14 686.5, 18 142.6)	286	16 250.1 (14 499.2, 18 212.4)

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

- a. Protocol-specified timing for blood sample collection.
- b. n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
- d. SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4-5).

Comirnaty 30 mcg

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

Efficacy in participants 16 years of age and older – after 2 doses

In the Phase 2/3 portion of Study 2, based on data accrued through 14 November 2020, approximately 44 000 participants were randomised equally and were to receive 2 doses of the initially approved COVID-19 mRNA Vaccine or placebo. The efficacy analyses included participants that received their

second vaccination within 19 to 42 days after their first vaccination. The majority (93.1%) of vaccine recipients received the second dose 19 days to 23 days after Dose 1. Participants are planned to be followed for up to 24 months after Dose 2, for assessments of safety and efficacy against COVID-19. In the clinical study, participants were required to observe a minimum interval of 14 days before and after administration of an influenza vaccine in order to receive either placebo or COVID-19 mRNA Vaccine. In the clinical study, participants were required to observe a minimum interval of 60 days before or after receipt of blood/plasma products or immunoglobulins within through conclusion of the study in order to receive either placebo or COVID-19 mRNA Vaccine.

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

At the time of the primary efficacy analysis, participants had been followed for symptomatic COVID-19 for in total 2 214 person-years for the COVID-19 mRNA Vaccine and in total 2 222 person-years in the placebo group.

There were no meaningful clinical differences in overall vaccine efficacy in participants who were at risk of severe COVID-19 including those with 1 or more comorbidities that increase the risk of severe COVID-19 (e.g. asthma, body mass index (BMI) ≥ 30 kg/m², chronic pulmonary disease, diabetes mellitus, hypertension).

The vaccine efficacy information is presented in Table 4.

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

First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection*			
Subgroup	COVID-19 mRNA Vaccine N^a = 18 198 Cases n1^b Surveillance time^c (n2^d)	Placebo N^a = 18 325 Cases n1^b Surveillance time^c (n2^d)	Vaccine efficacy % (95% CI)^e
All participants	8 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 5.

Table 5. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of prior SARS-CoV-2 infection* prior to 7 days after Dose 2 – evaluable efficacy (7 days) population during the placebo-controlled follow-up period

Subgroup	COVID-19 mRNA Vaccine N ^a =20 998 Cases n1 ^b Surveillance time ^c (n2 ^d)	Placebo N ^a =21 096 Cases n1 ^b Surveillance time ^c (n2 ^d)	Vaccine efficacy % (95% CI ^e)
All participants ^f	77 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 6) as the COVID-19 case counts in participants without prior SARS-CoV-2 infection were the same as those in participants with or without prior SARS-CoV-2 infection in both the COVID-19 mRNA Vaccine and placebo groups.

Table 6. Vaccine efficacy – First severe COVID-19 occurrence in participants with or without prior SARS-CoV-2 infection based on the Food and Drug Administration (FDA)* after Dose 1 or from 7 days after Dose 2 in the placebo-controlled follow-up

	COVID-19 mRNA Vaccine Cases n1 ^a Surveillance time (n2 ^b)	Placebo Cases n1 ^a Surveillance time (n2 ^b)	Vaccine efficacy % (95% CI) ^c
After Dose 1 ^d	1 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 $\leq 93\%$ on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen < 300 mm Hg);
 - Respiratory failure [defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
 - Evidence of shock (systolic blood pressure < 90 mm Hg, diastolic blood pressure < 60 mm Hg, or requiring vasopressors);
 - Significant acute renal, hepatic, or neurologic dysfunction;
 - Admission to an Intensive Care Unit;
 - Death.
- a. n1 = Number of participants meeting the endpoint definition.
 - b. n2 = Number of participants at risk for the endpoint.
 - c. Two-side confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
 - d. Efficacy assessed based on the Dose 1 all available efficacy (modified intention-to-treat) population that included all randomised participants who received at least 1 dose of study intervention.
 - e. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.

- f. Efficacy assessed based on the evaluable efficacy (7 Days) population that included all eligible randomised participants who receive all dose(s) of study intervention as randomised within the predefined window, have no other important protocol deviations as determined by the clinician.
- g. Total surveillance time in 1 000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

Efficacy and immunogenicity in adolescents 12 to 15 years of age – after 2 doses

In an initial analysis of Study 2 in adolescents 12 to 15 years of age (representing a median follow-up duration of > 2 months after Dose 2) without evidence of prior infection, there were no cases in 1 005 participants who received the vaccine and 16 cases out of 978 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 75.3, 100.0). In participants with or without evidence of prior infection there were 0 cases in the 1 119 who received vaccine and 18 cases in 1 110 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 78.1, 100.0).

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

In the updated efficacy analysis of Study 2 in adolescents 12 to 15 years of age without evidence of prior infection, there were no cases in 1 057 participants who received the vaccine and 28 cases out of 1 030 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 86.8, 100.0) during the period when Alpha variant was the predominant circulating strain. In participants with or without evidence of prior infection there were 0 cases in the 1 119 who received vaccine and 30 cases in 1 109 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 87.5, 100.0).

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

First COVID-19 occurrence from 7 days after booster dose in participants without evidence of prior SARS-CoV-2 infection*			
	Comirnaty N^a=4 695 Cases n1^b Surveillance Time^c (n2^d)	Placebo N^a=4 671 Cases n1^b Surveillance Time^c (n2^d)	Relative Vaccine Efficacy^e % (95% CI^f)
First COVID-19 occurrence from 7 days after booster vaccination	6 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.

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

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

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

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

pseudovirus (wild-type), neutralising antibody NT50 GMR-fold change increased 21.6-fold with heterologous Comirnaty booster (n = 95).

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

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

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

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

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

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

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

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

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

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

Note: Seroreponse is defined as achieving ≥ 4 -fold rise from baseline (before the study vaccination). If the baseline measurement is below the LLOQ, the post-vaccination measure of $\geq 4 \times \text{LLOQ}$ is considered a seroreponse.

- a. Protocol-specified timing for blood sample collection.
- b. N = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- c. N = Number of participants with valid and determinate assay results for the specified assay at both the pre-vaccination time point and the given sampling time point.
- d. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
- e. n = Number of participants with seroreponse for the given assay at the given sampling time point.
- f. Exact 2-sided CI, based on the Clopper and Pearson method.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Comirnaty in 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 neutralizing antibody responses were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in foetuses and offspring. There were no vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development. No Comirnaty data are available on vaccine placental transfer or excretion in milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened vial

Frozen vial

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

The vaccine will be received frozen at -90 °C to -60 °C. Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

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 or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Multidose vials

When stored frozen at -90 °C to -60 °C, 10-vial packs of multidose vials of the vaccine can be thawed at 2 °C to 8 °C for 6 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed vial

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

- Upon moving the vaccine to 2 °C to 8 °C storage, the updated expiry date must be written on the outer carton and the vaccine should be used or discarded by the updated expiry date. The original expiry date should be crossed out.
- If the vaccine is received at 2 °C to 8 °C it should be stored at 2 °C to 8 °C. The expiry date on the outer carton should have been updated to reflect the refrigerated expiry date and the original expiry date should have been crossed out.

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

Thawed vials can be handled in room light conditions.

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

Handling of temperature excursions during refrigerated storage

- Stability data indicate that the unopened vial is stable for up to 10 weeks when stored at temperatures from -2 °C to 2 °C, within the 10-week storage period between 2 °C and 8 °C.

- Stability data indicate the vial can be stored for up to 24 hours at temperatures of 8 °C to 30 °C, including up to 12 hours following first puncture.

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

Opened vial

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

6.4 Special precautions for storage

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

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

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

For storage conditions after thawing and first opening, see section 6.3.

6.5 Nature and contents of container

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

One single dose vial contains 1 dose of 0.3 mL, see sections 4.2 and 6.6.

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

Single dose vial pack size: 10 vials.

Multidose vial pack sizes: 10 vials or 195 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Handling instructions prior to use

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

- **Verify** that the vial has a **grey plastic cap** and the product **name is Comirnaty Omicron XBB.1.5 (30 micrograms)/dose dispersion for injection** (12 years and older).
- If the vial has another product name on the label, please make reference to the Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw. Ensure vials are completely thawed prior to use.
 - 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).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Preparation of 0.3 mL doses

- Gently mix by inverting vials 10 times prior to use. Do not shake.
 - Prior to mixing, the thawed dispersion may contain white to off-white opaque amorphous particles.
 - After mixing, the vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the vaccine if particulates or discoloration 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 Omicron XBB.1.5.
- 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 vial. Discard any unused vaccine 12 hours after first puncture.

Disposal

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

Single dose vials

EU/1/20/1528/018

Multidose vials

EU/1/20/1528/019

EU/1/20/1528/020

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 December 2020

Date of latest renewal: 10 October 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

▼ 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 Omicron XBB.1.5 10 micrograms/dose concentrate for dispersion for injection
COVID-19 mRNA Vaccine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

One vial (1.3 mL) contains 10 doses of 0.2 mL after dilution, see sections 4.2 and 6.6.

One dose (0.2 mL) contains 10 micrograms of raxtozinameran, a COVID-19 mRNA Vaccine (nucleoside modified, embedded in lipid nanoparticles).

Raxtozinameran is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 (Omicron XBB.1.5).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Comirnaty Omicron XBB.1.5 10 micrograms/dose concentrate for dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in children aged 5 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 Omicron XBB.1.5 10 micrograms/dose 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 Omicron XBB.1.5 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Severely immunocompromised aged 5 years and older

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

Comirnaty Omicron XBB.1.5 10 micrograms/dose should be used only for children 5 to 11 years of age.

Paediatric population

There are paediatric formulations available for infants and children aged 6 months to 4 years. For details, please refer to the 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 Omicron XBB.1.5 10 micrograms/dose concentrate for dispersion for injection should be administered intramuscularly after dilution (see section 6.6).

After dilution, vials of Comirnaty Omicron XBB.1.5 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.

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, hypoesthesia and sweating) may occur in association with the vaccination process itself. Stress-related reactions are temporary and resolve on their own. Individuals should be advised to bring symptoms to the attention of the vaccination provider for evaluation. It is important that precautions are in place to avoid injury from fainting.

Concurrent illness

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

Thrombocytopenia and coagulation disorders

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

Immunocompromised individuals

The efficacy and safety of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of Comirnaty Omicron XBB.1.5 may be lower in immunocompromised individuals.

Duration of protection

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

Limitations of vaccine effectiveness

As with any vaccine, vaccination with Comirnaty Omicron XBB.1.5 may not protect all vaccine recipients. Individuals may not be fully protected until 7 days after their vaccination.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concomitant administration of Comirnaty Omicron XBB.1.5 with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

No data are available yet regarding the use of Comirnaty Omicron XBB.1.5 during pregnancy.

However, a large amount of observational data from pregnant women vaccinated with the initially approved Comirnaty vaccine during the second and third trimester have not shown an increase in adverse pregnancy outcomes. While data on pregnancy outcomes following vaccination during the first trimester are presently limited, no increased risk for miscarriage has been seen. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development (see section 5.3). Based on data available with other vaccine variants, Comirnaty Omicron XBB.1.5 can be used during pregnancy.

Breast-feeding

No data are available yet regarding the use of Comirnaty Omicron XBB.1.5 during breast-feeding.

However, no effects on the breastfed newborn/infant are anticipated since the systemic exposure of breast-feeding woman to the vaccine is negligible. Observational data from women who were breast-feeding after vaccination with the initially approved Comirnaty vaccine have not shown a risk for adverse effects in breastfed newborns/infants. Comirnaty Omicron XBB.1.5 can be used during breast-feeding.

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of safety profile

The safety of Comirnaty Omicron XBB.1.5 is inferred from safety data of the prior Comirnaty vaccine.

Comirnaty

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

In Study 3, a total of 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 ($\geq 20\%$), myalgia, chills, and diarrhoea ($> 10\%$).

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

In a subset from Study 3, a total of 401 children 5 to 11 years of age received a booster dose of Comirnaty 10 mcg at least 5 months (range of 5 to 9 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 22 March 2022 (median follow-up time of 1.3 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 were injection site pain (> 70%), fatigue (> 40%), headache (> 30%), 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

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

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

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

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

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

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

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

Adverse reactions observed during clinical studies are listed below according to the following frequency categories: Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1\ 000$ to $< 1/100$), Rare ($\geq 1/10\ 000$ to $< 1/1\ 000$), Very rare ($< 1/10\ 000$), Not known (cannot be estimated from the available data).

Table 1. Adverse reactions from Comirnaty 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
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

- In participants 5 years of age and older, a higher frequency of lymphadenopathy was reported after a booster ($\leq 2.8\%$) dose than after primary ($\leq 0.9\%$) doses of the vaccine.
- The frequency category for urticaria and angioedema was rare.
- Through the clinical trial safety follow-up period to 14 November 2020, acute peripheral facial paralysis (or palsy) was reported by four participants in the COVID-19 mRNA Vaccine group. Onset was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.
- Adverse reaction determined post-authorisation.
- Refers to vaccinated arm.
- A higher frequency of pyrexia was observed after the second dose compared to the first dose.
- Facial swelling in vaccine recipients with a history of injection of dermatological fillers has been reported in the post-marketing phase.
- Injection site redness occurred at a higher frequency (very common) in children 5 to 11 years of age.
- Most cases appeared to be non-serious and temporary in nature.

Description of selected adverse reactions

Myocarditis and pericarditis

The increased risk of myocarditis after vaccination with Comirnaty is highest in younger males (see section 4.4).

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 listed in [Appendix V](#) and include batch/Lot number if available.

4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vaccines, viral vaccines, ATC code: J07BN01

Mechanism of action

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

Efficacy

Omicron-adapted Comirnaty

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

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

The immune response 1 month after a booster dose (fourth dose), Comirnaty Original/Omicron BA.4-5 elicited generally similar Omicron BA.4/BA.5-specific neutralizing titres compared with the titres in the comparator group who received 3 doses of Comirnaty. Comirnaty Original/Omicron BA.4-5 also elicited similar reference strain-specific titres compared with the titres in the comparator group.

The vaccine immunogenicity results after a booster dose in participants 5 to 11 years of age are presented in Table 2.

Table 2. Study 6 – Geometric mean ratio and Geometric mean titres – participants with or without evidence of infection – 5 to 11 years of age – evaluable immunogenicity population

SARS-CoV-2 neutralization assay	Sampling time point ^a	Vaccine Group (as Assigned/Randomized)				
		Study 6 Comirnaty (Original/Omicron BA.4/BA.5) 10 mcg Dose 4 and 1 Month After Dose 4		Study 3 Comirnaty 10 mcg Dose 3 and 1 Month After Dose 3		Study 6 Comirnaty (Original/Omicron BA.4/BA.5)/Comirnaty 10 mcg
		n ^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% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
- GMRs and 2-sided CIs were calculated by exponentiating the difference of LS Means for the assay and the corresponding CIs based on an analysis of log-transformed assay results using a linear regression model with baseline log-transformed neutralizing titers, postbaseline infection status, and vaccine group as covariates.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).

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

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

Analyses of 50% neutralizing antibody titres (NT50) against Omicron BA.4-5 and against reference strain among participants 56 years of age and older who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 in Study 5 compared to a subset of participants from Study 4 who received a booster (fourth dose) of Comirnaty demonstrated superiority of Comirnaty Original/Omicron BA.4-5 to Comirnaty based on geometric mean ratio (GMR) and noninferiority based on difference in seroresponse rates with respect to anti-Omicron BA.4-5 response, and noninferiority of anti-reference strain immune response based on GMR (Table 3).

Analyses of NT50 against Omicron BA.4/BA.5 among participants 18 through 55 years of age compared to participants 56 years of age and older who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 in Study 5 demonstrated noninferiority of anti-Omicron BA.4-5 response among participants 18 through 55 years of age compared to participants 56 years of age and older for both GMR and difference in seroresponse rates (Table 3).

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

Table 3. SARS-CoV-2 GMTs (NT50) and difference in percentages of participants with seroresponse at 1 month after vaccination course – Comirnaty Original/Omicron BA.4-5 from Study 5 and Comirnaty from subset of Study 4 – participants with or without evidence of SARS-CoV-2 infection – evaluable immunogenicity population

SARS-CoV-2 GMTs (NT50) at 1 month after vaccination course								
SARS-CoV-2 neutralization assay	Study 5 Comirnaty Original/Omicron BA.4-5				Subset of Study 4 Comirnaty		Age group comparison	Vaccine group comparison
	18 through 55 years of age		56 years of age and older		56 years of age and older		Comirnaty Original/Omicron BA.4-5 18 through 55 years of age/≥ 56 years of age	≥ 56 years of age Comirnaty Original/Omicron BA.4-5 /Comirnaty
	n ^a	GMT ^c (95% CI ^c)	n ^a	GMT ^b (95% CI ^b)	n ^a	GMT ^b (95% CI ^b)	GMR ^c (95% CI ^c)	GMR ^c (95% CI ^c)
Omicron BA.4-5 - NT50 (titre) ^d	297	4 455.9 (3 851.7, 5 154.8)	284	4 158.1 (3 554.8, 4 863.8)	282	938.9 (802.3, 1 098.8)	0.98 (0.83, 1.16) ^e	2.91 (2.45, 3.44) ^f
Reference Strain – NT50 (titre) ^d	-	-	286	16 250.1 (14 499.2, 18 212.4)	289	10 415.5 (9 366.7, 11 581.8)	-	1.38 (1.22, 1.56) ^g
Difference in percentages of participants with seroresponse at 1 month after vaccination course								
SARS-CoV-2 neutralization assay	Comirnaty Original/Omicron BA.4-5				Subset of Study 4 Comirnaty		Age group comparison	Vaccine group comparison
	18 through 55 years of age		56 years of age and older		56 years of age and older		Comirnaty Original/Omicron BA.4-5 18 through 55 years of age/≥ 56	Comirnaty Original/Omicron BA.4-5 /Comirnaty
	N ^h	n ⁱ (%) (95% CI ^k)	N ^h	n ⁱ (%) (95% CI ^k)	N ^h	n ⁱ (%) (95% CI ^k)	Difference ^k (95% CI ^l)	Difference ^k (95% CI ^l)
Omicron BA.4-5 - NT50 (titre) ^d	294	180 (61.2) (55.4, 66.8)	282	188 (66.7) (60.8, 72.1)	273	127 (46.5) (40.5, 52.6)	-3.03 (-9.68, 3.63) ^m	26.77 (19.59, 33.95) ⁿ

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

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

- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the difference of LS means and corresponding CIs based on analysis of logarithmically transformed neutralizing titres using a linear regression model with terms of baseline neutralizing titre (log scale) and vaccine group or age group.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).

- e. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67.
- f. Superiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 1.
- g. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥ 0.8 .
- h. N = Number of participants with valid and determinate assay results for the specified assay at both the prevaccination time point and the given sampling time point. This value is the denominator for the percentage calculation.
- i. n = Number of participants with seroresponse for the given assay at the given sampling time point.
- j. Exact 2-sided CI, based on the Clopper and Pearson method.
- k. Difference in proportions, expressed as a percentage.
- l. 2-sided CI based on the Miettinen and Nurminen method stratified by baseline neutralizing titre category (< median, \geq median) for the difference in proportions. The median of baseline neutralizing titres was calculated based on the pooled data in 2 comparator groups.
- m. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is $> -10\%$.
- n. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is $> -5\%$.

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

SARS-CoV-2 neutralization assay	Sampling time point ^a	Comirnaty Original/Omicron BA.4-5					
		12 through 17 years of age		18 through 55 years of age		56 years of age and older	
		n ^b	GMT ^c (95% CI ^c)	n ^b	GMT ^c (95% CI ^c)	n ^b	GMT ^c (95% CI ^c)
Omicron BA.4-5 - NT50 (titre) ^d	Pre-vaccination	104	1 105.8 (835.1, 1 464.3)	294	569.6 (471.4, 688.2)	284	458.2 (365.2, 574.8)
	1 month	105	8 212.8 (6 807.3, 9 908.7)	297	4 455.9 (3 851.7, 5 154.8)	284	4 158.1 (3 554.8, 4 863.8)
Reference Strain – NT50 (titre) ^d	Pre-vaccination	105	6 863.3 (5 587.8, 8 430.1)	296	4 017.3 (3 430.7, 4 704.1)	284	3 690.6 (3 082.2, 4 419.0)
	1 month	105	23 641.3 (20 473.1, 27 299.8)	296	16 323.3 (14 686.5, 18 142.6)	286	16 250.1 (14 499.2, 18 212.4)

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

- a. Protocol-specified timing for blood sample collection.
- b. n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
- d. SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4-5).

Comirnaty

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

Efficacy in participants 16 years of age and older – after 2 doses

In the Phase 2/3 portion of Study 2, based on data accrued through 14 November 2020, approximately 44 000 participants were randomised equally and were to receive 2 doses of the initially approved COVID-19 mRNA Vaccine or placebo. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. The majority (93.1%) of vaccine recipients received the second dose 19 days to 23 days after Dose 1. Participants are planned to be followed for up to 24 months after Dose 2, for assessments of safety and efficacy against COVID-19. In the clinical study, participants were required to observe a minimum interval of 14 days before and after administration of an influenza vaccine in order to receive either placebo or COVID-19 mRNA Vaccine. In the clinical study, participants were required to observe a minimum interval of 60 days before or after receipt of blood/plasma products or immunoglobulins within through conclusion of the study in order to receive either placebo or COVID-19 mRNA Vaccine.

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

At the time of the primary efficacy analysis, participants had been followed for symptomatic COVID-19 for in total 2 214 person-years for the COVID-19 mRNA Vaccine and in total 2 222 person-years in the placebo group.

There were no meaningful clinical differences in overall vaccine efficacy in participants who were at risk of severe COVID-19 including those with 1 or more comorbidities that increase the risk of severe COVID-19 (e.g. asthma, body mass index (BMI) ≥ 30 kg/m², chronic pulmonary disease, diabetes mellitus, hypertension).

The vaccine efficacy information is presented in Table 5.

Table 5. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of infection prior to 7 days after Dose 2 – evaluable efficacy (7 days) population

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 6.

Table 6. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of prior SARS-CoV-2 infection* prior to 7 days after Dose 2 – evaluable efficacy (7 days) population during the placebo-controlled follow-up period

Subgroup	COVID-19 mRNA Vaccine 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. n_2 = 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 7) as the COVID-19 case counts in participants without prior SARS-CoV-2 infection were the same as those in participants with or without prior SARS-CoV-2 infection in both the COVID-19 mRNA Vaccine and placebo groups.

Table 7. Vaccine efficacy – First severe COVID-19 occurrence in participants with or without prior SARS-CoV-2 infection based on the Food and Drug Administration (FDA)* after Dose 1 or from 7 days after Dose 2 in the placebo-controlled follow-up

	COVID-19 mRNA Vaccine Cases n_1^a Surveillance time (n_2^b)	Placebo Cases n_1^a Surveillance time (n_2^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 $\leq 93\%$ on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen < 300 mm Hg);
- Respiratory failure [defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
- Evidence of shock (systolic blood pressure < 90 mm Hg, diastolic blood pressure < 60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an Intensive Care Unit;
- Death.

- a. n_1 = Number of participants meeting the endpoint definition.
- b. n_2 = 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 8. No cases of COVID-19 were observed in either the vaccine group or the placebo group in participants with evidence of prior SARS-CoV-2 infection.

Table 8. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2: Without evidence of infection prior to 7 days after Dose 2 – Phase 2/3 – Children 5 to 11 years of age evaluable efficacy population

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.

- N = Number of participants in the specified group.
- n1 = Number of participants meeting the endpoint definition.
- 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.
- 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 prespecified immunobridging criteria for both the geometric mean ratio (GMR) and the seroresponse difference with seroresponse defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from baseline (before Dose 1).

The GMR of the SARS-CoV-2 NT50 1 month after Dose 2 in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) to that of young adults 16 to 25 years of age was 1.04 (2-sided 95% CI: 0.93, 1.18). Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, 99.2% of children 5 to 11 years of age and 99.2% of participants 16 to 25 years of age had a seroresponse at 1 month after Dose 2. The difference in proportions of participants who had seroresponse between the 2 age groups (children – young adult) was 0.0% (2-sided 95% CI: -2.0%, 2.2%). This information is presented in Table 9.

Table 9. Summary of geometric mean ratio for 50% neutralising titre and difference in percentages of participants with seroresponse – comparison of children 5 to 11 years of age (Study 3) to participants 16 to 25 years of age (Study 2) – participants without evidence of infection up to 1 month after Dose 2 – immunobridging subset – Phase 2/3 – evaluable immunogenicity population

		COVID-19 mRNA Vaccine		5 to 11 years/ 16 to 25 years	
		10 mcg/dose 5 to 11 years N ^a =264	30 mcg/dose 16 to 25 years N ^a =253		
	Time point ^b	GMT ^c (95% CI ^e)	GMT ^c (95% CI ^e)	GMR ^d (95% CI ^d)	Met immunobridging objective ^e (Y/N)
Geometric mean 50% neutralizing 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% neutralizing 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 postvaccination assay result $\geq 4 \times$ LLOQ is considered a seroresponse.

- N = Number of participants with valid and determinate assay results before vaccination and at 1 month after Dose 2. These values are also the denominators used in the percentage calculations for seroresponse rates.
- Protocol-specified timing for blood sample collection.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (5 to 11 years of age minus 16 to 25 years of age) and the corresponding CI (based on the Student t distribution).
- Immunobridging based on GMT is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥ 0.8 .
- SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralisation is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralised.
- n = Number of participants with seroresponse based on NT50 1 month after Dose 2.
- Exact 2-sided CI based on the Clopper and Pearson method.
- Difference in proportions, expressed as a percentage (5 to 11 years of age minus 16 to 25 years of age).
- 2-Sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
- Immunobridging based on seroresponse rate is declared if the lower bound of the 2-sided 95% CI for the seroresponse difference is greater than -10.0%.

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

A booster dose of Comirnaty was given to 401 randomly selected participants in Study 3. Effectiveness of a booster dose in ages 5 to 11 is inferred by immunogenicity. The immunogenicity of this was assessed through NT50 against the reference strain of SARS-CoV-2 (USA_WA1/2020). Analyses of NT50 1 month after the booster dose compared to before the booster dose demonstrated a substantial increase in GMTs in individuals 5 through 11 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the dose 2 and the booster dose. This analysis is summarized in Table 10.

Table 10. Summary of geometric mean titres – NT50 – participants without evidence of infection – phase 2/3 – immunogenicity set – 5 through 11 years of age – evaluable immunogenicity population

Assay	Sampling time point ^a		1 month after booster dose/ 1 month after dose 2
	1 month after booster dose (n ^b =67)	1 month after dose 2 (n ^b =96)	
	GMT ^c (95% CI ^c)	GMT ^c (95% CI ^c)	GMR ^d (95% CI ^d)
SARS-CoV-2 neutralization 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% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

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

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Comirnaty in 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 neutralizing antibody responses were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in foetuses and offspring. There were no vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development. No Comirnaty data are available on vaccine placental transfer or excretion in milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

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

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

Cholesterol

Trometamol

Trometamol hydrochloride

Sucrose

Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial

Frozen vial

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

The vaccine will be received frozen at -90 °C to -60 °C. Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

When stored frozen at -90 °C to -60 °C, 10-vial packs of the vaccine can be thawed at 2 °C to 8 °C for 4 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed vial

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

- Upon moving the vaccine to 2 °C to 8 °C storage, the updated expiry date must be written on the outer carton and the vaccine should be used or discarded by the updated expiry date. The original expiry date should be crossed out.

- If the vaccine is received at 2 °C to 8 °C it should be stored at 2 °C to 8 °C. The expiry date on the outer carton should have been updated to reflect the refrigerated expiry date and the original expiry date should have been crossed out.

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

Thawed vials can be handled in room light conditions.

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

Handling of temperature excursions during refrigerated storage

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

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

Diluted medicinal product

Chemical and physical in-use stability has been demonstrated for 12 hours at 2 °C to 30 °C, after dilution with sodium chloride 9 mg/mL (0.9%) solution for injection, which includes up to 6 hours transportation time. From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

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

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

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

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

6.5 Nature and contents of container

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

6.6 Special precautions for disposal and other handling

Handling instructions prior to use

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

- **Verify** that the vial has an **orange plastic cap** and the product **name is Comirnaty Omicron XBB.1.5 (10 micrograms)/dose concentrate for dispersion for injection** (children 5 to 11 years).
- If the vial has another product name on the label, please make reference to the Summary of Product Characteristics 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 4 hours to thaw. Ensure vials are completely thawed prior to use.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Dilution

- 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 **1.3 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 1.3 mL air into the empty diluent syringe.
- Gently invert the diluted dispersion 10 times. Do not shake.
- The diluted vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discolouration are present.
- The diluted vials should be marked with the appropriate **discard date and time**.
- **After dilution**, store at 2 °C to 30 °C and use within **12 hours**.
- Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.

Preparation of 0.2 mL doses

- 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 Omicron XBB.1.5 for children aged 5 to 11 years. **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 12 hours after dilution.

Disposal

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

7. MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz
Germany
Phone: +49 6131 9084-0
Fax: +49 6131 9084-2121
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8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1528/021

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 December 2020
Date of latest renewal: 10 October 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

▼ 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 Omicron XBB.1.5 10 micrograms/dose dispersion for injection
COVID-19 mRNA Vaccine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

One single dose vial contains 1 dose of 0.3 mL, see sections 4.2 and 6.6.

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

One dose (0.3 mL) contains 10 micrograms of raxtozinameran, a COVID-19 mRNA Vaccine (nucleoside modified, embedded in lipid nanoparticles).

Raxtozinameran is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 (Omicron XBB.1.5).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersion for injection.

The vaccine is a clear to slightly opalescent frozen dispersion (pH: 6.9 - 7.9).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Comirnaty Omicron XBB.1.5 10 micrograms/dose dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in children aged 5 to 11 years.

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 Omicron XBB.1.5 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 Omicron XBB.1.5 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Severely immunocompromised aged 5 years and older

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

Comirnaty Omicron XBB.1.5 10 micrograms/dose should be used only for children 5 to 11 years of age.

Paediatric population

There are paediatric formulations available for infants and children aged 6 months to 4 years. For details, please refer to the 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 Omicron XBB.1.5 10 micrograms/dose dispersion for injection should be administered intramuscularly (see section 6.6). Do not dilute prior to use.

The preferred site is the deltoid muscle of the upper arm.

Do not inject the vaccine intravascularly, subcutaneously or intradermally.

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

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

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

Single dose vials

Single dose vials of Comirnaty Omicron XBB.1.5 contain 1 dose of 0.3 mL of vaccine.

- Withdraw a single 0.3 mL dose of Comirnaty Omicron XBB.1.5.
- Discard vial and any excess volume.
- Do not pool excess vaccine from multiple vials.

Multidose vials

Multidose vials of Comirnaty Omicron XBB.1.5 contain 6 doses of 0.3 mL of vaccine. In order to extract 6 doses from a single vial, low dead-volume syringes and/or needles should be used. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial. Irrespective of the type of syringe and needle:

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Traceability

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

General recommendations

Hypersensitivity and anaphylaxis

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

Close observation for at least 15 minutes is recommended following vaccination. No further dose of the vaccine should be given to those who have experienced anaphylaxis after a prior dose of Comirnaty.

Myocarditis and pericarditis

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

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

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

Anxiety-related reactions

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

Concurrent illness

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

Thrombocytopenia and coagulation disorders

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

Immunocompromised individuals

The efficacy and safety of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of Comirnaty Omicron XBB.1.5 may be lower in immunocompromised individuals.

Duration of protection

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

Limitations of vaccine effectiveness

As with any vaccine, vaccination with Comirnaty Omicron XBB.1.5 may not protect all vaccine recipients. Individuals may not be fully protected until 7 days after their vaccination.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concomitant administration of Comirnaty Omicron XBB.1.5 with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

No data are available yet regarding the use of Comirnaty Omicron XBB.1.5 during pregnancy.

However, a large amount of observational data from pregnant women vaccinated with the initially approved Comirnaty vaccine during the second and third trimester have not shown an increase in adverse pregnancy outcomes. While data on pregnancy outcomes following vaccination during the first trimester are presently limited, no increased risk for miscarriage has been seen. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development (see section 5.3). Based on data available with other vaccine variants, Comirnaty Omicron XBB.1.5 can be used during pregnancy.

Breast-feeding

No data are available yet regarding the use of Comirnaty Omicron XBB.1.5 during breast-feeding.

However, no effects on the breastfed newborn/infant are anticipated since the systemic exposure of breast-feeding woman to the vaccine is negligible. Observational data from women who were breast-feeding after vaccination with the initially approved Comirnaty vaccine have not shown a risk for adverse effects in breastfed newborns/infants. Comirnaty Omicron XBB.1.5 can be used during breast-feeding.

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of safety profile

The safety of Comirnaty Omicron XBB.1.5 is inferred from safety data of the prior Comirnaty 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 ($\geq 20\%$), myalgia, chills, and diarrhoea ($> 10\%$).

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

In a subset from Study 3, a total of 401 children 5 to 11 years of age received a booster dose of Comirnaty 10 mcg at least 5 months (range of 5 to 9 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 22 March 2022 (median follow-up time of 1.3 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 were injection site pain ($> 70\%$), fatigue ($> 40\%$), headache ($> 30\%$), 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

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

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

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

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

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

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

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

Adverse reactions observed during clinical studies are listed below according to the following frequency categories: Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1\ 000$ to $< 1/100$), Rare ($\geq 1/10\ 000$ to $< 1/1\ 000$), Very rare ($< 1/10\ 000$), Not known (cannot be estimated from the available data).

Table 1. Adverse reactions from Comirnaty 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
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

- In participants 5 years of age and older, a higher frequency of lymphadenopathy was reported after a booster ($\leq 2.8\%$) dose than after primary ($\leq 0.9\%$) doses of the vaccine.
- The frequency category for urticaria and angioedema was rare.
- Through the clinical trial safety follow-up period to 14 November 2020, acute peripheral facial paralysis (or palsy) was reported by four participants in the COVID-19 mRNA Vaccine group. Onset was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.
- Adverse reaction determined post-authorisation.
- Refers to vaccinated arm.
- A higher frequency of pyrexia was observed after the second dose compared to the first dose.
- Facial swelling in vaccine recipients with a history of injection of dermatological fillers has been reported in the post-marketing phase.
- Injection site redness occurred at a higher frequency (very common) in children 5 to 11 years of age.
- Most cases appeared to be non-serious and temporary in nature.

Description of selected adverse reactions

Myocarditis and pericarditis

The increased risk of myocarditis after vaccination with Comirnaty is highest in younger males (see section 4.4).

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 listed in [Appendix V](#) and include batch/Lot number if available.

4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vaccines, viral vaccines, ATC code: J07BN01

Mechanism of action

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

Efficacy

Omicron-adapted Comirnaty

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

In an analysis of a subset from Study 6, 103 participants 5 to 11 years of age who had previously received a 2-dose primary series and booster dose with Comirnaty received a booster (fourth dose) of

Comirnaty Original/Omicron BA.4-5. Results include immunogenicity data from a comparator subset of participants 5 to 11 years of age in Study 3 who received 3 doses of Comirnaty. In participants 5 to 11 years of age who received a fourth dose of Comirnaty Original/Omicron BA.4-5 and participants 5 to 11 years of age who received a third dose of Comirnaty, 57.3% and 58.4% were positive for SARS-CoV-2 at baseline, respectively.

The immune response 1 month after a booster dose (fourth dose), Comirnaty Original/Omicron BA.4-5 elicited generally similar Omicron BA.4/BA.5-specific neutralizing titres compared with the titres in the comparator group who received 3 doses of Comirnaty. Comirnaty Original/Omicron BA.4-5 also elicited similar reference strain-specific titres compared with the titres in the comparator group.

The vaccine immunogenicity results after a booster dose in participants 5 to 11 years of age are presented in Table 2.

Table 2. Study 6 – Geometric mean ratio and Geometric mean titres – participants with or without evidence of infection – 5 to 11 years of age – evaluable immunogenicity population

SARS-CoV-2 neutralization assay	Sampling time point ^a	Vaccine Group (as Assigned/Randomized)				
		Study 6 Comirnaty (Original/Omicron BA.4/BA.5) 10 mcg Dose 4 and 1 Month After Dose 4		Study 3 Comirnaty 10 mcg Dose 3 and 1 Month After Dose 3		Study 6 Comirnaty (Original/Omicron BA.4/BA.5)/Comirnaty 10 mcg
		n ^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% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
- GMRs and 2-sided CIs were calculated by exponentiating the difference of LS Means for the assay and the corresponding CIs based on analysis of log-transformed assay results using a linear regression model with baseline log-transformed neutralizing titers, postbaseline infection status, and vaccine group as covariates.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).

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

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

Analyses of 50% neutralizing antibody titres (NT50) against Omicron BA.4-5 and against reference strain among participants 56 years of age and older who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 in Study 5 compared to a subset of participants from Study 4 who received a booster (fourth dose) of Comirnaty demonstrated superiority of Comirnaty Original/Omicron BA.4-5 to Comirnaty based on geometric mean ratio (GMR) and noninferiority based on difference in seroresponse rates with respect to anti-Omicron BA.4-5 response, and noninferiority of anti-reference strain immune response based on GMR (Table 3).

Analyses of NT50 against Omicron BA.4/BA.5 among participants 18 through 55 years of age compared to participants 56 years of age and older who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 in Study 5 demonstrated noninferiority of anti-Omicron BA.4-5 response among participants 18 through 55 years of age compared to participants 56 years of age and older for both GMR and difference in seroresponse rates (Table 3).

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

Table 3. SARS-CoV-2 GMTs (NT50) and difference in percentages of participants with seroresponse at 1 month after vaccination course – Comirnaty Original/Omicron BA.4-5 from Study 5 and Comirnaty from subset of Study 4 – participants with or without evidence of SARS-CoV-2 infection – evaluable immunogenicity population

SARS-CoV-2 GMTs (NT50) at 1 month after vaccination course									
SARS-CoV-2 neutralization assay	Study 5 Comirnaty Original/Omicron BA.4-5				Subset of Study 4 Comirnaty		Age group comparison	Vaccine group comparison	
	18 through 55 years of age		56 years of age and older		56 years of age and older		Comirnaty Original/Omicron BA.4-5 18 through 55 years of age/≥ 56 years of age	≥ 56 years of age Comirnaty Original/Omicron BA.4-5 /Comirnaty	
	n ^a	GMT ^c (95% CI ^c)	n ^a	GMT ^b (95% CI ^b)	n ^a	GMT ^b (95% CI ^b)	GMR ^c (95% CI ^c)	GMR ^c (95% CI ^c)	
	Omicron BA.4-5 - NT50 (titre) ^d	297	4 455.9 (3 851.7, 5 154.8)	284	4 158.1 (3 554.8, 4 863.8)	282	938.9 (802.3, 1 098.8)	0.98 (0.83, 1.16) ^e	2.91 (2.45, 3.44) ^f
Reference Strain – NT50 (titre) ^d	-	-	286	16 250.1 (14 499.2, 18 212.4)	289	10 415.5 (9 366.7, 11 581.8)	-	1.38 (1.22, 1.56) ^g	
Difference in percentages of participants with seroresponse at 1 month after vaccination course									
SARS-CoV-2 neutralization assay	Comirnaty Original/Omicron BA.4-5				Subset of Study 4 Comirnaty		Age group comparison	Vaccine group comparison	
	18 through 55 years of age		56 years of age and older		56 years of age and older		Comirnaty Original/Omicron BA.4-5 18 through 55 years of age/≥ 56	≥ 56 years of age Comirnaty Original/Omicron BA.4-5 /Comirnaty	
	N ^h	n ⁱ (%) (95% CI ^k)	N ^h	n ⁱ (%) (95% CI ^k)	N ^h	n ⁱ (%) (95% CI ^j)	Difference ^k (95% CI ^l)	Difference ^k (95% CI ^l)	
	Omicron BA.4-5 - NT50 (titre) ^d	294	180 (61.2) (55.4, 66.8)	282	188 (66.7) (60.8, 72.1)	273	127 (46.5) (40.5, 52.6)	-3.03 (-9.68, 3.63) ^m	26.77 (19.59, 33.95) ⁿ

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

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

- a. n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- b. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
- c. GMRs and 2-sided 95% CIs were calculated by exponentiating the difference of LS means and corresponding CIs based on analysis of logarithmically transformed neutralizing titres using a linear regression model with terms of baseline neutralizing titre (log scale) and vaccine group or age group.
- d. SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).
- e. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67.
- f. Superiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 1.
- g. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥ 0.8 .
- h. N = Number of participants with valid and determinate assay results for the specified assay at both the prevaccination time point and the given sampling time point. This value is the denominator for the percentage calculation.
- i. n = Number of participants with seroresponse for the given assay at the given sampling time point.
- j. Exact 2-sided CI, based on the Clopper and Pearson method.
- k. Difference in proportions, expressed as a percentage.
- l. 2-sided CI based on the Miettinen and Nurminen method stratified by baseline neutralizing titre category ($<$ median, \geq median) for the difference in proportions. The median of baseline neutralizing titres was calculated based on the pooled data in 2 comparator groups.
- m. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is $> -10\%$.
- n. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is $> -5\%$.

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

SARS-CoV-2 neutralization assay	Sampling time point ^a	Comirnaty Original/Omicron BA.4-5					
		12 through 17 years of age		18 through 55 years of age		56 years of age and older	
		n ^b	GMT ^c (95% CI ^c)	n ^b	GMT ^c (95% CI ^c)	n ^b	GMT ^c (95% CI ^c)
Omicron BA.4-5 - NT50 (titre) ^e	Pre-vaccination	104	1 105.8 (835.1, 1 464.3)	294	569.6 (471.4, 688.2)	284	458.2 (365.2, 574.8)
	1 month	105	8 212.8 (6 807.3, 9 908.7)	297	4 455.9 (3 851.7, 5 154.8)	284	4 158.1 (3 554.8, 4 863.8)
Reference Strain – NT50 (titre) ^d	Pre-vaccination	105	6 863.3 (5 587.8, 8 430.1)	296	4 017.3 (3 430.7, 4 704.1)	284	3 690.6 (3 082.2, 4 419.0)
	1 month	105	23 641.3 (20 473.1, 27 299.8)	296	16 323.3 (14 686.5, 18 142.6)	286	16 250.1 (14 499.2, 18 212.4)

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

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4-5).

Comirnaty

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

Efficacy in participants 16 years of age and older – after 2 doses

In the Phase 2/3 portion of Study 2, based on data accrued through 14 November 2020, approximately 44 000 participants were randomised equally and were to receive 2 doses of the initially approved COVID-19 mRNA Vaccine or placebo. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. The majority (93.1%) of vaccine recipients received the second dose 19 days to 23 days after Dose 1. Participants are planned to be followed for up to 24 months after Dose 2, for assessments of safety and efficacy against COVID-19. In the clinical study, participants were required to observe a minimum interval of 14 days before and after administration of an influenza vaccine in order to receive either placebo or COVID-19 mRNA Vaccine. In the clinical study, participants were required to observe a minimum interval of 60 days before or after receipt of blood/plasma products or immunoglobulins within through conclusion of the study in order to receive either placebo or COVID-19 mRNA Vaccine.

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

mRNA Vaccine group and 68 in the placebo group) and 1 616 participants 75 years of age and older (804 in the COVID-19 mRNA Vaccine group and 812 in the placebo group).

At the time of the primary efficacy analysis, participants had been followed for symptomatic COVID-19 for in total 2 214 person-years for the COVID-19 mRNA Vaccine and in total 2 222 person-years in the placebo group.

There were no meaningful clinical differences in overall vaccine efficacy in participants who were at risk of severe COVID-19 including those with 1 or more comorbidities that increase the risk of severe COVID-19 (e.g. asthma, body mass index (BMI) ≥ 30 kg/m², chronic pulmonary disease, diabetes mellitus, hypertension).

The vaccine efficacy information is presented in Table 5.

Table 5. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of infection prior to 7 days after Dose 2 – evaluable efficacy (7 days) population

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 n^{1b} Surveillance time^c (n^{2d})	Placebo N^a = 18 325 Cases n^{1b} Surveillance time^c (n^{2d})	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 6.

Table 6. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of prior SARS-CoV-2 infection* prior to 7 days after Dose 2 – evaluable efficacy (7 days) population during the placebo-controlled follow-up period

Subgroup	COVID-19 mRNA Vaccine 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.

- N = Number of participants in the specified group.
- n1 = Number of participants meeting the endpoint definition.
- 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.
- n2 = Number of participants at risk for the endpoint.
- Two-sided 95% confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
- Included confirmed cases in participants 12 to 15 years of age: 0 in the COVID-19 mRNA Vaccine group; 16 in the placebo group.

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

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

Efficacy against severe COVID-19

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

As of 13 March 2021, vaccine efficacy against severe COVID-19 is presented only for participants with or without prior SARS-CoV-2 infection (Table 7) as the COVID-19 case counts in participants without prior SARS-CoV-2 infection were the same as those in participants with or without prior SARS-CoV-2 infection in both the COVID-19 mRNA Vaccine and placebo groups.

Table 7. Vaccine efficacy – First severe COVID-19 occurrence in participants with or without prior SARS-CoV-2 infection based on the Food and Drug Administration (FDA)* after Dose 1 or from 7 days after Dose 2 in the placebo-controlled follow-up

	COVID-19 mRNA Vaccine 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 $\leq 93\%$ on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen < 300 mm Hg);
- Respiratory failure [defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
- Evidence of shock (systolic blood pressure < 90 mm Hg, diastolic blood pressure < 60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an Intensive Care Unit;
- Death.

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

b. n2 = Number of participants at risk for the endpoint.

c. Two-side confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.

d. Efficacy assessed based on the Dose 1 all available efficacy (modified intention-to-treat) population that included all randomised participants who received at least 1 dose of study intervention.

e. Total surveillance time in 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 8. No cases of COVID-19 were observed in either the vaccine group or the placebo group in participants with evidence of prior SARS-CoV-2 infection.

Table 8. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2: Without evidence of infection prior to 7 days after Dose 2 – Phase 2/3 – Children 5 to 11 years of age evaluable efficacy population

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 n^{1b} Surveillance time^c (n^{2d})	Placebo N^a=663 Cases n^{1b} Surveillance time^c (n^{2d})	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 prespecified immunobridging criteria for both the geometric mean ratio (GMR) and the seroresponse difference with seroresponse defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from baseline (before Dose 1).

The GMR of the SARS-CoV-2 NT50 1 month after Dose 2 in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) to that of young adults 16 to 25 years of age was 1.04 (2-sided 95% CI: 0.93, 1.18). Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, 99.2% of children 5 to 11 years of age and 99.2% of participants 16 to 25 years of age had a seroresponse at 1 month after Dose 2. The difference in proportions of participants who had seroresponse between the 2 age groups (children – young adult) was 0.0% (2-sided 95% CI: -2.0%, 2.2%). This information is presented in Table 9.

Table 9. Summary of geometric mean ratio for 50% neutralising titre and difference in percentages of participants with seroresponse – comparison of children 5 to 11 years of age (Study 3) to participants 16 to 25 years of age (Study 2) – participants without evidence of infection up to 1 month after Dose 2 – immunobridging subset – Phase 2/3 – evaluable immunogenicity population

		COVID-19 mRNA Vaccine		5 to 11 years/ 16 to 25 years	
		10 mcg/dose 5 to 11 years N ^a =264	30 mcg/dose 16 to 25 years N ^a =253		
	Time point ^b	GMT ^c (95% CI ^f)	GMT ^c (95% CI ^f)	GMR ^d (95% CI ^d)	Met immunobridging objective ^e (Y/N)
Geometric mean 50% neutralizing 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% neutralizing 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 postvaccination assay result $\geq 4 \times$ LLOQ is considered a seroresponse.

- N = Number of participants with valid and determinate assay results before vaccination and at 1 month after Dose 2. These values are also the denominators used in the percentage calculations for seroresponse rates.
- Protocol-specified timing for blood sample collection.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (5 to 11 years of age minus 16 to 25 years of age) and the corresponding CI (based on the Student t distribution).
- Immunobridging based on GMT is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥ 0.8 .
- SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralisation is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralised.
- n = Number of participants with seroresponse based on NT50 1 month after Dose 2.
- Exact 2-sided CI based on the Clopper and Pearson method.
- Difference in proportions, expressed as a percentage (5 to 11 years of age minus 16 to 25 years of age).
- 2-Sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
- Immunobridging based on seroresponse rate is declared if the lower bound of the 2-sided 95% CI for the seroresponse difference is greater than -10.0%.

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

A booster dose of Comirnaty was given to 401 randomly selected participants in Study 3. Effectiveness of a booster dose in ages 5 to 11 is inferred by immunogenicity. The immunogenicity of this was assessed through NT50 against the reference strain of SARS-CoV-2 (USA_WA1/2020). Analyses of NT50 1 month after the booster dose compared to before the booster dose demonstrated a substantial increase in GMTs in individuals 5 through 11 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the dose 2 and the booster dose. This analysis is summarized in Table 10.

Table 10. Summary of geometric mean titres – NT50 – participants without evidence of infection – phase 2/3 – immunogenicity set – 5 through 11 years of age – evaluable immunogenicity population

Assay	Sampling time point ^a		1 month after booster dose/ 1 month after dose 2
	1 month after booster dose (n ^b =67)	1 month after dose 2 (n ^b =96)	
	GMT ^c (95% CI ^c)	GMT ^c (95% CI ^c)	GMR ^d (95% CI ^d)
SARS-CoV-2 neutralization 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% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

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

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Comirnaty in 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 neutralizing antibody responses were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in foetuses and offspring. There were no vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development. No Comirnaty data are available on vaccine placental transfer or excretion in milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened vial

Frozen vial

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

The vaccine will be received frozen at -90 °C to -60 °C. Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

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 or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Multidose vials

When stored frozen at -90 °C to -60 °C, 10-vial packs of multidose vials of the vaccine can be thawed at 2 °C to 8 °C for 6 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed vial

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

- Upon moving the vaccine to 2 °C to 8 °C storage, the updated expiry date must be written on the outer carton and the vaccine should be used or discarded by the updated expiry date. The original expiry date should be crossed out.
- If the vaccine is received at 2 °C to 8 °C it should be stored at 2 °C to 8 °C. The expiry date on the outer carton should have been updated to reflect the refrigerated expiry date and the original expiry date should have been crossed out.

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

Thawed vials can be handled in room light conditions.

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

Handling of temperature excursions during refrigerated storage

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

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

Opened vial

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

6.4 Special precautions for storage

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

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

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

For storage conditions after thawing and first opening, see section 6.3.

6.5 Nature and contents of container

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

One single dose vial contains 1 dose of 0.3 mL, see sections 4.2 and 6.6.

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

Single dose vial pack size: 10 vials.

Multidose vial pack size: 10 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Handling instructions prior to use

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

- **Verify that the vial has a blue plastic cap and the product name is Comirnaty Omicron XBB.1.5 (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 Summary of Product Characteristics for that formulation.

- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw. Ensure vials are completely thawed prior to use.
 - 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).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Preparation of 0.3 mL doses

- Gently mix by inverting vials 10 times prior to use. Do not shake.
- Prior to mixing, the thawed dispersion may contain white to off-white opaque amorphous particles.
- After mixing, the vaccine should present as a clear to slightly opalescent dispersion with no particulates visible. Do not use the vaccine if particulates or discoloration 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 Omicron XBB.1.5 for children aged 5 to 11 years.

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 vial. Discard any unused vaccine 12 hours after first puncture.

Disposal

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

7. **MARKETING AUTHORISATION HOLDER**

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

8. MARKETING AUTHORISATION NUMBER(S)

Single dose vials

EU/1/20/1528/022

Multidose vials

EU/1/20/1528/023

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 December 2020

Date of latest renewal: 10 October 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

▼ 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 Omicron XBB.1.5 3 micrograms/dose concentrate for dispersion for injection
COVID-19 mRNA Vaccine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

One vial (0.4 mL) contains 10 doses of 0.2 mL after dilution, see sections 4.2 and 6.6.

One dose (0.2 mL) contains 3 micrograms of raxtozinameran, a COVID-19 mRNA Vaccine (nucleoside modified, embedded in lipid nanoparticles).

Raxtozinameran is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 (Omicron XBB.1.5).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Comirnaty Omicron XBB.1.5 3 micrograms/dose concentrate for dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in infants and children aged 6 months to 4 years.

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 Omicron XBB.1.5 3 micrograms/dose is administered intramuscularly after dilution as a primary course of 3 doses (0.2 mL each). It is recommended to administer the second dose 3 weeks after the first dose followed by a third dose administered at least 8 weeks after the second dose (see sections 4.4 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 Omicron XBB.1.5 3 micrograms/dose is administered intramuscularly after dilution as a single dose of 0.2 mL for infants and children 6 months to 4 years of age.

For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty Omicron XBB.1.5 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Severely immunocompromised aged 6 months to 4 years

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

Interchangeability

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

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

Paediatric population

There are paediatric formulations available for children 5 to 11 years of age. For details, please refer to the 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 Omicron XBB.1.5 3 micrograms/dose concentrate for dispersion for injection should be administered intramuscularly after dilution (see section 6.6).

After dilution, vials of Comirnaty Omicron XBB.1.5 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.

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

The efficacy and safety of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of Comirnaty Omicron XBB.1.5 may be lower in immunocompromised individuals.

Duration of protection

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

Limitations of vaccine effectiveness

As with any vaccine, vaccination with Comirnaty Omicron XBB.1.5 may not protect all vaccine recipients. Individuals may not be fully protected until 7 days after their vaccination.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concomitant administration of Comirnaty Omicron XBB.1.5 with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation

Comirnaty Omicron XBB.1.5 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 Omicron XBB.1.5 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 Omicron XBB.1.5 is inferred from safety data of the prior Comirnaty vaccines.

Comirnaty

Infants 6 to 23 months of age – after 3 doses

In an analysis of Study 3 (Phase 2/3), 1 776 infants (1 178 initially approved Comirnaty 3 mcg and 598 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 29 April 2022, 570 infants 6 to 23 months of age who received a 3-dose primary course (386 Comirnaty 3 mcg and 184 placebo) have been followed for a median of 1.3 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), 2 750 children (1 835 Comirnaty 3 mcg and 915 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 29 April 2022, 886 children 2 to 4 years of age who received a 3-dose primary course

(606 Comirnaty 3 mcg and 280 placebo) have been followed a median of 1.4 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 Comirnaty 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 \geq 4 months after the second dose in the placebo-controlled blinded follow-up period. The safety evaluation in Study 3 is ongoing.

The overall safety profile of Comirnaty in participants 5 to 11 years of age was similar to that seen in participants 16 years of age and older. The most frequent adverse reactions in children 5 to 11 years of age that received 2 doses were injection site pain (> 80%), fatigue (> 50%), headache (> 30%), injection site redness and swelling (\geq 20%), myalgia, chills and diarrhoea (> 10%).

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

In a subset from Study 3, a total of 401 children 5 to 11 years of age received a booster dose of Comirnaty 10 mcg at least 5 months (range of 5 to 9 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 22 March 2022 (median follow-up time of 1.3 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 were injection site pain (> 70%), fatigue (> 40%), headache (> 30%), 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 \geq 4 months after the second dose.

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

Participants 16 years of age and older – after 2 doses

In Study 2, a total of 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 \geq 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 a subset from Study 6 (Phase 3), 39 participants 6 to 23 months of age who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (1.5/1.5 mcg) 2.1 to 8.6 months after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 had a median follow-up time of at least 1.7 months.

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

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

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

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

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

In a subset from Study 6 (Phase 3), 113 participants 5 to 11 years of age who had completed 3 doses of Comirnaty, received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 (5/5 mcg) 2.6 to

8.5 months after receiving Dose 3. Participants who received a booster (fourth dose) of Comirnaty Original/Omicron BA.4-5 had a median follow-up time of at least 1.6 months.

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

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

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

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

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

Adverse reactions observed during clinical studies are listed below according to the following frequency categories: Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1\ 000$ to $< 1/100$), Rare ($\geq 1/10\ 000$ to $< 1/1\ 000$), Very rare ($< 1/10\ 000$), Not known (cannot be estimated from the available data).

Table 1. Adverse reactions from Comirnaty 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
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

System Organ Class	Frequency	Adverse reactions
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 ($\leq 2.8\%$) dose than after primary ($\leq 0.9\%$) doses of the vaccine.
- b. The frequency category for angioedema was rare.
- c. Through the clinical trial safety follow-up period to 14 November 2020, acute peripheral facial paralysis (or palsy) was reported by four participants in the COVID-19 mRNA Vaccine group. Onset was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.
- d. Adverse reaction determined post-authorization.
- e. Refers to vaccinated arm.
- f. A higher frequency of pyrexia was observed after the second dose compared to the first dose.
- g. Facial swelling in vaccine recipients with a history of injection of dermatological fillers has been reported in the post-marketing phase.
- h. Injection site redness occurred at a higher frequency (very common) in participants 6 months to 11 years of age.
- i. The frequency category for rash was common in participants 6 to 23 months of age.
- j. The frequency category for decreased appetite was very common in participants 6 to 23 months of age.
- k. Irritability, injection site tenderness, and drowsiness pertain to participants 6 to 23 months of age.
- l. Most cases appeared to be non-serious and temporary in nature.

Description of selected adverse reactions

Myocarditis and pericarditis

The increased risk of myocarditis after vaccination with Comirnaty is highest in younger males (see section 4.4).

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 listed in [Appendix V](#) and include batch/Lot number if available.

4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vaccines, viral vaccines, ATC code: J07BN01

Mechanism of action

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

Efficacy

Omicron-adapted Comirnaty

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

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

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

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

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

SARS-CoV-2 neutralization assay	Age group	Sampling time point ^a	Vaccine group (as assigned/randomized)			
			Study 6 Comirnaty Original/Omicron BA.4-5 1.5/1.5 mcg Dose 4 and 1 month after Dose 4		Study 3 Comirnaty 3 mcg Dose 3 and 1 month after Dose 3	
			n ^b	GMT ^c (95% CI ^c)	n ^b	GMT ^c (95% CI ^c)
Omicron BA.4-5 - NT50 (titre) ^d	6 months through 4 years	Pre-vaccination	54	192.5 (120.4, 307.8)	54	70.5 (51.1, 97.2)
		1 month	58	1 695.2 (1 151.8, 2 494.9)	54	607.9 (431.1, 857.2)
Reference strain - NT50 (titre) ^d	6 months through 4 years	Pre-vaccination	57	2 678.1 (1 913.0, 3 749.2)	53	776.8 (536.4, 1 125.0)
		1 month	58	9 733.0 (7 708.2, 12 289.6)	53	9 057.3 (7 223.4, 11 356.8)

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

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).

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

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

The immune response 1 month after a booster dose (fourth dose), Comirnaty Original/Omicron BA.4-5 elicited generally similar Omicron BA.4/BA.5-specific neutralizing titres compared with the titres in the comparator group who received 3 doses of Comirnaty. Comirnaty Original/Omicron BA.4-5 also elicited similar reference strain-specific titres compared with the titres in the comparator group.

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

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

SARS-CoV-2 neutralization assay	Sampling time point ^a	Vaccine group (as assigned/randomized)				
		Study 6 Comirnaty (Original/Omicron BA.4/BA.5) 10 mcg Dose 4 and 1 month after Dose 4		Study 3 Comirnaty 10 mcg Dose 3 and 1 month after Dose 3		Study 6 Comirnaty (Original/Omicron BA.4/BA.5)/Comirnaty 10 mcg
		n ^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% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.

- d. GMRs and 2-sided CIs were calculated by exponentiating the difference of LS Means for the assay and the corresponding CIs based on an analysis of log-transformed assay results using a linear regression model with baseline log-transformed neutralizing titers, postbaseline infection status, and vaccine group as covariates.
- e. SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).

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

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

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

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

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

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

SARS-CoV-2 GMTs (NT50) at 1 month after vaccination course								
SARS-CoV-2 neutralization assay	Study 5 Comirnaty Original/Omicron BA.4-5				Subset of Study 4 Comirnaty		Age group comparison	Vaccine group comparison
	18 through 55 years of age		56 years of age and older		56 years of age and older		Comirnaty Original/Omicron BA.4-5 18 through 55 years of age/≥56 years of age	≥56 years of age Comirnaty Original/Omicron BA.4-5 /Comirnaty
	n ^a	GMT ^c (95% CI ^c)	n ^a	GMT ^b (95% CI ^b)	n ^a	GMT ^b (95% CI ^b)	GMR ^c (95% CI ^c)	GMR ^c (95% CI ^c)
	Omicron BA.4-5 - NT50 (titre) ^d	297	4 455.9 (3 851.7, 5 154.8)	284	4 158.1 (3 554.8, 4 863.8)	282	938.9 (802.3, 1 098.8)	0.98 (0.83, 1.16) ^e
Reference Strain – NT50 (titre) ^d	-	-	286	16 250.1 (14 499.2, 18 212.4)	289	10 415.5 (9 366.7, 11 581.8)	-	1.38 (1.22, 1.56) ^g

Difference in percentages of participants with seroresponse at 1 month after vaccination course								
	Comirnaty Original/Omicron BA.4-5				Subset of Study 4 Comirnaty		Age group comparison	Vaccine group comparison ≥ 56 years of age
	18 through 55 years of age		56 years of age and older		56 years of age and older		Comirnaty Original/Omicron BA.4-5 18 through 55 years of age/ ≥ 56	Comirnaty Original/Omicron BA.4-5 /Comirnaty
SARS-CoV-2 neutralization assay	N ^h	n ⁱ (%) (95% CI ^k)	N ^h	n ⁱ (%) (95% CI ^k)	N ^h	n ⁱ (%) (95% CI ^l)	Difference ^k (95% CI ^l)	Difference ^k (95% CI ^l)
Omicron BA.4-5 - NT50 (titre) ^d	294	180 (61.2) (55.4, 66.8)	282	188 (66.7) (60.8, 72.1)	273	127 (46.5) (40.5, 52.6)	-3.03 (-9.68, 3.63) ^m	26.77 (19.59, 33.95) ⁿ

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

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

- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the difference of LS means and corresponding CIs based on analysis of logarithmically transformed neutralizing titres using a linear regression model with terms of baseline neutralizing titre (log scale) and vaccine group or age group.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).
- Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67.
- Superiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 1.
- Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥ 0.8 .
- N = Number of participants with valid and determinate assay results for the specified assay at both the prevaccination time point and the given sampling time point. This value is the denominator for the percentage calculation.
- n = Number of participants with seroresponse for the given assay at the given sampling time point.
- Exact 2-sided CI, based on the Clopper and Pearson method.
- Difference in proportions, expressed as a percentage.
- 2-sided CI based on the Miettinen and Nurminen method stratified by baseline neutralizing titre category (< median, \geq median) for the difference in proportions. The median of baseline neutralizing titres was calculated based on the pooled data in 2 comparator groups.
- Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is $> -10\%$.
- Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is $> -5\%$.

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

SARS-CoV-2 neutralization assay	Sampling time point ^a	Comirnaty Original/Omicron BA.4-5					
		12 through 17 years of age		18 through 55 years of age		56 years of age and older	
		n ^b	GMT ^c (95% CI ^c)	n ^b	GMT ^c (95% CI ^c)	n ^b	GMT ^c (95% CI ^c)
Omicron BA.4-5 - NT50 (titre) ^d	Pre-vaccination	104	1 105.8 (835.1, 1 464.3)	294	569.6 (471.4, 688.2)	284	458.2 (365.2, 574.8)
	1 month	105	8 212.8 (6 807.3, 9 908.7)	297	4 455.9 (3 851.7, 5 154.8)	284	4 158.1 (3 554.8, 4 863.8)
Reference strain - NT50 (titre) ^d	Pre-vaccination	105	6 863.3 (5 587.8, 8 430.1)	296	4 017.3 (3 430.7, 4 704.1)	284	3 690.6 (3 082.2, 4 419.0)
	1 month	105	23 641.3 (20 473.1, 27 299.8)	296	16 323.3 (14 686.5, 18 142.6)	286	16 250.1 (14 499.2, 18 212.4)

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

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4-5).

Comirnaty

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

Efficacy in participants 16 years of age and older – after 2 doses

In the Phase 2/3 portion of Study 2, based on data accrued through 14 November 2020, approximately 44 000 participants were randomised equally and were to receive 2 doses of the initially approved COVID-19 mRNA Vaccine or placebo. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. The majority (93.1%) of vaccine recipients received the second dose 19 days to 23 days after Dose 1. Participants are planned to be followed for up to 24 months after Dose 2, for assessments of safety and efficacy against COVID-19. In the clinical study, participants were required to observe a minimum interval of 14 days before and after administration of an influenza vaccine in order to receive either placebo or COVID-19 mRNA Vaccine. In the clinical study, participants were required to observe a minimum interval of 60 days before or after receipt of blood/plasma products or immunoglobulins within through conclusion of the study in order to receive either placebo or COVID-19 mRNA Vaccine.

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

mRNA Vaccine group and 68 in the placebo group) and 1 616 participants 75 years of age and older (804 in the COVID-19 mRNA Vaccine group and 812 in the placebo group).

At the time of the primary efficacy analysis, participants had been followed for symptomatic COVID-19 for in total 2 214 person-years for the COVID-19 mRNA Vaccine and in total 2 222 person-years in the placebo group.

There were no meaningful clinical differences in overall vaccine efficacy in participants who were at risk of severe COVID-19 including those with 1 or more comorbidities that increase the risk of severe COVID-19 (e.g. asthma, body mass index (BMI) \geq 30 kg/m², chronic pulmonary disease, diabetes mellitus, hypertension).

The vaccine efficacy information is presented in Table 6.

Table 6. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of infection prior to 7 days after Dose 2 – evaluable efficacy (7 days) population

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 n^{1b} Surveillance time^c (n^{2d})	Placebo N^a = 18 325 Cases n^{1b} Surveillance time^c (n^{2d})	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 7.

Table 7. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of prior SARS-CoV-2 infection* prior to 7 days after Dose 2 – evaluable efficacy (7 days) population during the placebo-controlled follow-up period

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.

- N = Number of participants in the specified group.
- n1 = Number of participants meeting the endpoint definition.
- 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.
- n2 = Number of participants at risk for the endpoint.
- Two-sided 95% confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
- Included confirmed cases in participants 12 to 15 years of age: 0 in the COVID-19 mRNA Vaccine group; 16 in the placebo group.

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

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

Efficacy against severe COVID-19

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

As of 13 March 2021, vaccine efficacy against severe COVID-19 is presented only for participants with or without prior SARS-CoV-2 infection (Table 8) as the COVID-19 case counts in participants without prior SARS-CoV-2 infection were the same as those in participants with or without prior SARS-CoV-2 infection in both the COVID-19 mRNA Vaccine and placebo groups.

Table 8. Vaccine efficacy – First severe COVID-19 occurrence in participants with or without prior SARS-CoV-2 infection based on the Food and Drug Administration (FDA)* after Dose 1 or from 7 days after Dose 2 in the placebo-controlled follow-up

	COVID-19 mRNA Vaccine Cases n1 ^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 $\leq 93\%$ on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen < 300 mm Hg);
- Respiratory failure [defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
- Evidence of shock (systolic blood pressure < 90 mm Hg, diastolic blood pressure < 60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an Intensive Care Unit;
- Death.

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

b. n2 = Number of participants at risk for the endpoint.

c. Two-side confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.

d. Efficacy assessed based on the Dose 1 all available efficacy (modified intention-to-treat) population that included all randomised participants who received at least 1 dose of study intervention.

e. Total surveillance time in 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 9. No cases of COVID-19 were observed in either the vaccine group or the placebo group in participants with evidence of prior SARS-CoV-2 infection.

Table 9. Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2: Without evidence of infection prior to 7 days after Dose 2 – Phase 2/3 – Children 5 to 11 years of age evaluable efficacy population

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 n^{1b} Surveillance time^c (n^{2d})	Placebo N^a=663 Cases n^{1b} Surveillance time^c (n^{2d})	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 prespecified immunobridging criteria for both the geometric mean ratio (GMR) and the seroresponse difference with seroresponse defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from baseline (before Dose 1).

The GMR of the SARS-CoV-2 NT50 1 month after Dose 2 in children 5 to 11 years of age (i.e. 5 to less than 12 years of age) to that of young adults 16 to 25 years of age was 1.04 (2-sided 95% CI: 0.93, 1.18). Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, 99.2% of children 5 to 11 years of age and 99.2% of participants 16 to 25 years of age had a seroresponse at 1 month after Dose 2. The difference in proportions of participants who had seroresponse between the 2 age groups (children – young adult) was 0.0% (2-sided 95% CI: -2.0%, 2.2%). This information is presented in Table 10.

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

		COVID-19 mRNA Vaccine		5 to 11 years/ 16 to 25 years	
		10 mcg/dose 5 to 11 years N ^a =264	30 mcg/dose 16 to 25 years N ^a =253		
	Time point ^b	GMT ^c (95% CI ^e)	GMT ^c (95% CI ^e)	GMR ^d (95% CI ^d)	Met immunobridging objective ^e (Y/N)
Geometric mean 50% neutralizing 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% neutralizing 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 postvaccination assay result $\geq 4 \times$ LLOQ is considered a seroresponse.

- N = Number of participants with valid and determinate assay results before vaccination and at 1 month after Dose 2. These values are also the denominators used in the percentage calculations for seroresponse rates.
- Protocol-specified timing for blood sample collection.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (5 to 11 years of age minus 16 to 25 years of age) and the corresponding CI (based on the Student t distribution).
- Immunobridging based on GMT is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥ 0.8 .
- SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralisation is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralised.
- n = Number of participants with seroresponse based on NT50 1 month after Dose 2.
- Exact 2-sided CI based on the Clopper and Pearson method.
- Difference in proportions, expressed as a percentage (5 to 11 years of age minus 16 to 25 years of age).
- 2-Sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
- Immunobridging based on seroresponse rate is declared if the lower bound of the 2-sided 95% CI for the seroresponse difference is greater than -10.0%.

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

A booster dose of Comirnaty was given to 401 randomly selected participants in Study 3. Effectiveness of a booster dose in ages 5 to 11 is inferred by immunogenicity. The immunogenicity of this was assessed through NT50 against the reference strain of SARS-CoV-2 (USA_WA1/2020). Analyses of NT50 1 month after the booster dose compared to before the booster dose demonstrated a substantial increase in GMTs in individuals 5 through 11 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the dose 2 and the booster dose. This analysis is summarized in Table 11.

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

Assay	Sampling time point ^a		
	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 neutralization 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% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

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

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

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

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

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

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 n ^{1b} Surveillance Time ^c (n2 ^d)	Placebo N ^a =381 Cases n ^{1b} Surveillance Time ^c (n2 ^d)	Vaccine Efficacy % (95% CI ^e)
6 months through 4 years ^e	13 0.124 (794)	21 0.054 (351)	73.2 (43.8, 87.6)
2 through 4 years	9 0.081 (498)	13 0.033 (204)	71.8 (28.6, 89.4)
6 months through 23 months	4 0.042 (296)	8 0.020 (147)	75.8 (9.7, 94.7)

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

- * Participants who had no serological or virological evidence (prior to 7 days after receipt of Dose 3) of past SARS-CoV-2 infection (i.e. negative N-binding antibody [serum] result at Dose 1, 1 month post-Dose 2 (if available), Dose 3 (if available) visits, SARS-CoV-2 not detected by NAAT [nasal swab] at Dose 1, Dose 2, and Dose 3 study visits, and a negative NAAT [nasal swab] result at any unscheduled visit prior to 7 days after receipt of Dose 3) and had no medical history of COVID-19 were included in the analysis.
 - 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 through 23 months of age, severe COVID-19 criteria were fulfilled for 3 cases (2 COVID-19 mRNA Vaccine and 1 placebo).

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

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

The primary immunobridging analyses compared the geometric mean titres (using a geometric mean ratio [GMR]) and the seroresponse (defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from before Dose 1) rates in the evaluable immunogenicity population of participants without evidence of prior SARS-CoV-2 infection up to 1 month after Dose 3 in participants 6 to 23 months of age and 2 to 4 years of age and up to 1 month after Dose 2 in participants 16 to 25 years of age. The prespecified immunobridging criteria were met for both the GMR and the seroresponse difference for both age groups (Table 13).

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

SARS-CoV-2 GMTs (NT50) at 1 month after vaccination course							
SARS-CoV-2 neutralization 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 neutralization 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) ^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 postvaccination assay result $\geq 4 \times$ LLOQ is considered a seroresponse.

- N = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point for GMTs and number of participants with valid and determinate assay results for the specified assay at both baseline and the given dose/sampling time point for seroresponse rates.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (younger age group minus 16 to 25 years of age) and the corresponding CI (based on the Student t distribution).

- d. For each younger age group (2 to 4 years, 6 to 23 months), immunobridging based on GMR is declared if the lower bound of the 2-sided 95% CI for the GMR ratio is greater than 0.67 and the point estimate of the GMR is ≥ 0.8 .
- e. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralisation Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralised.
- f. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.
- g. Exact 2-sided CI based on the Clopper and Pearson method.
- h. Difference in proportions, expressed as a percentage (younger age group minus 16 to 25 years of age).
- i. 2-sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
- j. For each younger age group (2 to 4 years, 6 to 23 months), immunobridging based on seroresponse rate is declared if the lower bound of the 2-sided 95% CI for the difference in proportions is greater than -10.0% provided that the immunobridging criteria based on GMR were met.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Comirnaty in 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 neutralizing antibody responses were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in foetuses and offspring. There were no vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development. No Comirnaty data are available on vaccine placental transfer or excretion in milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial

Frozen vial

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

The vaccine will be received frozen at -90 °C to -60 °C. Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

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

Thawed vial

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

- Upon moving the vaccine to 2 °C to 8 °C storage, the updated expiry date must be written on the outer carton and the vaccine should be used or discarded by the updated expiry date. The original expiry date should be crossed out.
- If the vaccine is received at 2 °C to 8 °C it should be stored at 2 °C to 8 °C. The expiry date on the outer carton should have been updated to reflect the refrigerated expiry date and the original expiry date should have been crossed out.

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

Thawed vials can be handled in room light conditions.

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

Handling of temperature excursions during refrigerated storage

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

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

Diluted medicinal product

Chemical and physical in-use stability has been demonstrated for 12 hours at 2 °C to 30 °C, after dilution with sodium chloride 9 mg/mL (0.9%) solution for injection, which includes up to 6 hours transportation time. From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

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

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

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

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

6.5 Nature and contents of container

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

6.6 Special precautions for disposal and other handling

Handling instructions prior to use

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

- **Verify** that the vial has a **maroon plastic cap** and the product **name is Comirnaty Omicron XBB.1.5 (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, please make reference to the Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 10-vial pack may take 2 hours to thaw. Ensure vials are completely thawed prior to use.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Dilution

- 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 **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 2.2 mL air into the empty diluent syringe.

- Gently invert the diluted dispersion 10 times. Do not shake.
- The diluted vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discolouration are present.
- The diluted vials should be marked with the appropriate **discard date and time**.
- **After dilution**, store at 2 °C to 30 °C and use within **12 hours**.
- Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.

Preparation of 0.2mL doses

- 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 Omicron XBB.1.5 for infants and children aged 6 months to 4 years.
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 12 hours after dilution.

Disposal

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1528/024

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 December 2020
Date of latest renewal: 10 October 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCES AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCES AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance(s)

BioNTech Manufacturing Marburg GmbH
Emil-von-Behring-Strasse 76
35041 Marburg
Germany

Pfizer Ireland Pharmaceuticals
Grange Castle Business Park
Clondalkin
Dublin 22
Ireland

Wyeth BioPharma Division of Wyeth Pharmaceuticals LLC
1 Burtt Road
Andover, MA 01810
USA

Name and address of the manufacturers responsible for batch release

BioNTech Manufacturing GmbH
Kupferbergterrasse 17 - 19
55116 Mainz
Germany

Pfizer Manufacturing Belgium NV
Rijksweg 12
Puurs-Sint-Amands, 2870
Belgium

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

- **Official batch release**

In accordance with Article 114 of Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOX LABEL

1. NAME OF THE MEDICINAL PRODUCT

COMIRNATY 30 micrograms/dose concentrate for dispersion for injection
adults and adolescents from 12 years
COVID-19 mRNA Vaccine
tozinameran

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After dilution, each vial contains 6 doses of 0.3 mL.

3. LIST OF EXCIPIENTS

Excipients: ALC-0315, ALC-0159, DSPC, cholesterol, potassium chloride, potassium dihydrogen phosphate, sodium chloride, disodium phosphate dihydrate, sucrose, water for injections, sodium hydroxide, hydrochloric acid

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for dispersion for injection
195 multidose vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use after dilution.
Read the package leaflet before use.



Scan for more information.
www.comirnatyglobal.com

Before use, dilute each vial with 1.8 mL sodium chloride 9 mg/mL (0.9%) solution for injection.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (at -90 °C to -60 °C)
Expiry date at 2 °C to 8 °C:
(Maximum 1 month. Cross out former expiry date.)

9. SPECIAL STORAGE CONDITIONS

Prior to dilution, store at -90 °C to -60 °C in the original package in order to protect from light.
After dilution, store at 2 °C to 30 °C and use within 6 hours.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1528/001

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

COMIRNATY 30 mcg sterile concentrate
COVID-19 mRNA Vaccine
tozinameran
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6 doses 30 mcg after dilution

6. OTHER

Discard time:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON (10 vials)
BOX LABEL (195 vials)

1. NAME OF THE MEDICINAL PRODUCT

COMIRNATY 30 micrograms/dose dispersion for injection
adults and adolescents from 12 years
COVID-19 mRNA Vaccine
tozinameran

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Single dose vials

Each vial contains 1 dose of 0.3 mL.

Multidose vials

Each vial contains 6 doses of 0.3 mL.

3. LIST OF EXCIPIENTS

Excipients: ALC-0315, ALC-0159, DSPC, cholesterol, trometamol, trometamol hydrochloride, sucrose, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for injection

Single dose vials

10 single dose vials

Multidose vials

10 multidose vials

195 multidose vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use.
Do not dilute prior to use.
Read the package leaflet before use.



Scan for more information.
www.comirnatyglobal.com

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (at -90 °C to -60 °C)
Expiry date at 2 °C to 8 °C:
(Maximum 10 weeks. Cross out former expiry date.)

9. SPECIAL STORAGE CONDITIONS

Store at 2 °C to 8 °C after receipt. Do not refreeze.
Store in the original package in order to protect from light.

Multidose vials

After first puncture, store at 2 °C to 30 °C and use within 12 hours.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

12. MARKETING AUTHORISATION NUMBER(S)

Single dose vials
EU/1/20/1528/013

Multidose vials
EU/1/20/1528/002 10 multidose vials
EU/1/20/1528/003 195 multidose vials

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

COMIRNATY 30 mcg injection
COVID-19 mRNA Vaccine
tozinameran
IM

2. METHOD OF ADMINISTRATION

Do not dilute

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Single dose vials
1 dose

Multidose vials
6 doses 30 mcg

6. OTHER

Multidose vials
Discard time:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON (10 vials)
BOX LABEL (195 vials)

1. NAME OF THE MEDICINAL PRODUCT

COMIRNATY 10 micrograms/dose concentrate for dispersion for injection
children 5 to 11 years
COVID-19 mRNA Vaccine
tozinameran

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After dilution, each vial contains 10 doses of 0.2 mL.

3. LIST OF EXCIPIENTS

Excipients: ALC-0315, ALC-0159, DSPC, cholesterol, trometamol, trometamol hydrochloride, sucrose, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for dispersion for injection
10 multidose vials
195 multidose vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use after dilution.
Read the package leaflet before use.



Scan for more information.
www.comirnatyglobal.com

Before use, dilute each vial with 1.3 mL sodium chloride 9 mg/mL (0.9%) solution for injection.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (at -90 °C to -60 °C)
Expiry date at 2 °C to 8 °C:
(Maximum 10 weeks. Cross out former expiry date.)

9. SPECIAL STORAGE CONDITIONS

Store at 2 °C to 8 °C after receipt. Do not refreeze.
Store in the original package in order to protect from light.
After dilution, store at 2 °C to 30 °C and use within 12 hours.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1528/004 10 multidose vials
EU/1/20/1528/005 195 multidose vials

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

COMIRNATY 10 mcg sterile concentrate
COVID-19 mRNA Vaccine
tozinameran
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 doses 10 mcg after dilution

6. OTHER

Discard time:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

COMIRNATY 3 micrograms/dose concentrate for dispersion for injection
children 6 months to 4 years
COVID-19 mRNA Vaccine
tozinameran

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After dilution, each vial contains 10 doses of 0.2 mL.

3. LIST OF EXCIPIENTS

Excipients: ALC-0315, ALC-0159, DSPC, cholesterol, trometamol, trometamol hydrochloride, sucrose, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for dispersion for injection
10 multidose vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use after dilution.
Read the package leaflet before use.



Scan for more information.
www.comirnatyglobal.com

Before use, dilute each vial with 2.2 mL sodium chloride 9 mg/mL (0.9%) solution for injection.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (at -90 °C to -60 °C)
Expiry date at 2 °C to 8 °C:
(Maximum 10 weeks. Cross out former expiry date.)

9. SPECIAL STORAGE CONDITIONS

Store at 2 °C to 8 °C after receipt. Do not refreeze.
Store in the original package in order to protect from light.
After dilution, store at 2 °C to 30 °C and use within 12 hours.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1528/010

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

COMIRNATY 3 mcg sterile concentrate
COVID-19 mRNA Vaccine
tozinameran
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 doses 3 mcg after dilution

6. OTHER

Discard time:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON (10 vials)
BOX LABEL (195 vials)

1. NAME OF THE MEDICINAL PRODUCT

COMIRNATY Original/Omicron BA.1 (15/15 micrograms)/dose dispersion for injection
adults and adolescents from 12 years
COVID-19 mRNA Vaccine
tozinameran/riltozinameran

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 6 doses of 0.3 mL.
One dose contains 15 micrograms tozinameran and 15 micrograms riltozinameran.

3. LIST OF EXCIPIENTS

Excipients: ALC-0315, ALC-0159, DSPC, cholesterol, trometamol, trometamol hydrochloride, sucrose, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for injection
10 multidose vials
195 multidose vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use.
Do not dilute prior to use.
Read the package leaflet before use.



Scan for more information.
www.comirnatyglobal.com

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (at -90 °C to -60 °C)
Expiry date at 2 °C to 8 °C:
(Maximum 10 weeks. Cross out former expiry date.)

9. SPECIAL STORAGE CONDITIONS

Store at 2 °C to 8 °C after receipt. Do not refreeze.
Store in the original package in order to protect from light.
After first puncture, store at 2 °C to 30 °C and use within 12 hours.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1528/006 10 multidose vials
EU/1/20/1528/007 195 multidose vials

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

COMIRNATY Original/Omicron BA.1 15/15 mcg injection
COVID-19 mRNA Vaccine
tozinameran/riltozinameran
IM

2. METHOD OF ADMINISTRATION

Do not dilute

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6 doses 15/15 mcg

6. OTHER

Discard time:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON (10 vials)
BOX LABEL (195 vials)

1. NAME OF THE MEDICINAL PRODUCT

COMIRNATY Original/Omicron BA.4-5 (15/15 micrograms)/dose dispersion for injection
adults and adolescents from 12 years
COVID-19 mRNA Vaccine
tozinameran/famtozinameran

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One dose contains 15 micrograms tozinameran and 15 micrograms famtozinameran.

Single dose vials

Each vial contains 1 dose of 0.3 mL.

Multidose vials

Each vial contains 6 doses of 0.3 mL.

3. LIST OF EXCIPIENTS

Excipients: ALC-0315, ALC-0159, DSPC, cholesterol, trometamol, trometamol hydrochloride, sucrose, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for injection

Single dose vials

10 single dose vials

Multidose vials

10 multidose vials

195 multidose vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use.
Do not dilute prior to use.
Read the package leaflet before use.



Scan for more information.
www.comirnatyglobal.com

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (at -90 °C to -60 °C)
Expiry date at 2 °C to 8 °C:
(Maximum 10 weeks. Cross out former expiry date.)

9. SPECIAL STORAGE CONDITIONS

Store at 2 °C to 8 °C after receipt. Do not refreeze.
Store in the original package in order to protect from light.

Multidose vials

After first puncture, store at 2 °C to 30 °C and use within 12 hours.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

12. MARKETING AUTHORISATION NUMBER(S)

Single dose vials
EU/1/20/1528/014

Multidose vials
EU/1/20/1528/008 10 multidose vials
EU/1/20/1528/009 195 multidose vials

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

COMIRNATY Original/Omicron BA.4-5 15/15 mcg injection
COVID-19 mRNA Vaccine
tozinameran/famtozinameran
IM

2. METHOD OF ADMINISTRATION

Do not dilute

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Single dose vials

1 dose

Multidose vials

6 doses 15/15 mcg

6. OTHER

Multidose vials

Discard time:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON (10 vials)
BOX LABEL (195 vials)

1. NAME OF THE MEDICINAL PRODUCT

COMIRNATY Original/Omicron BA.4-5 (5/5 micrograms)/dose concentrate for dispersion for injection
children 5 to 11 years
COVID-19 mRNA Vaccine
tozinameran/famtozinameran

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After dilution, each vial contains 10 doses of 0.2 mL.
One dose contains 5 micrograms tozinameran and 5 micrograms famtozinameran.

3. LIST OF EXCIPIENTS

Excipients: ALC-0315, ALC-0159, DSPC, cholesterol, trometamol, trometamol hydrochloride, sucrose, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for dispersion for injection
10 multidose vials
195 multidose vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use after dilution.
Read the package leaflet before use.



Scan for more information.
www.comirnatyglobal.com

Before use, dilute each vial with 1.3 mL sodium chloride 9 mg/mL (0.9%) solution for injection.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (at -90 °C to -60 °C)
Expiry date at 2 °C to 8 °C:
(Maximum 10 weeks. Cross out former expiry date.)

9. SPECIAL STORAGE CONDITIONS

Store at 2 °C to 8 °C after receipt. Do not refreeze.
Store in the original package in order to protect from light.
After dilution, store at 2 °C to 30 °C and use within 12 hours.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1528/011 10 multidose vials
EU/1/20/1528/012 195 multidose vials

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

COMIRNATY Original/Omicron BA.4-5 5/5 mcg sterile concentrate
COVID-19 mRNA Vaccine
tozinameran/famtozinameran
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 doses 5/5 mcg after dilution

6. OTHER

Discard time:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

COMIRNATY Original/Omicron BA.4-5 (5/5 micrograms)/dose dispersion for injection
children 5 to 11 years
COVID-19 mRNA Vaccine
tozinameran/famtozinameran

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One dose contains 5 micrograms tozinameran and 5 micrograms famtozinameran.

Single dose vials

Each vial contains 1 dose of 0.3 mL.

Multidose vials

Each vial contains 6 doses of 0.3 mL.

3. LIST OF EXCIPIENTS

Excipients: ALC-0315, ALC-0159, DSPC, cholesterol, trometamol, trometamol hydrochloride, sucrose, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for injection

Single dose vials

10 single dose vials

Multidose vials

10 multidose vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use.
Do not dilute prior to use.
Read the package leaflet before use.



Scan code for more information.
www.comirnatyglobal.com

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (at -90 °C to -60 °C)
Expiry date at 2 °C to 8 °C:
(Maximum 10 weeks. Cross out former expiry date.)

9. SPECIAL STORAGE CONDITIONS

Store at 2 °C to 8 °C after receipt. Do not refreeze.
Store in the original package in order to protect from light.

Multidose vials

After first puncture, store at 2 °C to 30 °C and use within 12 hours.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

12. MARKETING AUTHORISATION NUMBER(S)

Single dose vials
EU/1/20/1528/015

Multidose vials
EU/1/20/1528/016

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

COMIRNATY Original/Omicron BA.4-5 5/5 mcg injection
COVID-19 mRNA Vaccine
tozinameran/famtozinameran
IM

2. METHOD OF ADMINISTRATION

Do not dilute

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Single dose vials

1 dose

Multidose vials

6 doses 5/5 mcg

6. OTHER

Multidose vials

Discard time:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

COMIRNATY Original/Omicron BA.4-5 (1.5/1.5 micrograms)/dose concentrate for dispersion for injection
children 6 months to 4 years
COVID-19 mRNA Vaccine
tozinameran/famtozinameran

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After dilution, each vial contains 10 doses of 0.2 mL.
One dose contains 1.5 micrograms tozinameran and 1.5 micrograms famtozinameran.

3. LIST OF EXCIPIENTS

Excipients: ALC-0315, ALC-0159, DSPC, cholesterol, trometamol, trometamol hydrochloride, sucrose, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for dispersion for injection
10 multidose vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use after dilution.
Read the package leaflet before use.



Scan for more information.
www.comirnatyglobal.com

Before use, dilute each vial with 2.2 mL sodium chloride 9 mg/mL (0.9%) solution for injection.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (at -90 °C to -60 °C)
Expiry date at 2 °C to 8 °C:
(Maximum 10 weeks. Cross out former expiry date.)

9. SPECIAL STORAGE CONDITIONS

Store at 2 °C to 8 °C after receipt. Do not refreeze.
Store in the original package in order to protect from light.
After dilution, store at 2 °C to 30 °C and use within 12 hours.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1528/017

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

COMIRNATY Original/Omicron BA.4-5 1.5/1.5 mcg sterile concentrate
COVID-19 mRNA Vaccine
tozinameran/famtozinameran
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 doses 1.5/1.5 mcg after dilution

6. OTHER

Discard time:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON (10 vials)
BOX LABEL (195 vials)

1. NAME OF THE MEDICINAL PRODUCT

COMIRNATY Omicron XBB.1.5 30 micrograms/dose dispersion for injection
adults and adolescents from 12 years
COVID-19 mRNA Vaccine
raxtozinameran

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One dose contains 30 micrograms raxtozinameran.

Single dose vials

Each vial contains 1 dose of 0.3 mL.

Multidose vials

Each vial contains 6 doses of 0.3 mL.

3. LIST OF EXCIPIENTS

Excipients: ALC-0315, ALC-0159, DSPC, cholesterol, trometamol, trometamol hydrochloride, sucrose, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for injection

Single dose vials

10 single dose vials

Multidose vials

10 multidose vials

195 multidose vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use.
Do not dilute prior to use.
Read the package leaflet before use.



Scan for more information.
www.comirnatyglobal.com

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (at -90 °C to -60 °C)
Expiry date at 2 °C to 8 °C:
(Maximum 10 weeks. Cross out former expiry date.)

9. SPECIAL STORAGE CONDITIONS

Store at 2 °C to 8 °C after receipt. Do not refreeze.
Store in the original package in order to protect from light.

Multidose vials

After first puncture, store at 2 °C to 30 °C and use within 12 hours.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

12. MARKETING AUTHORISATION NUMBER(S)

Single dose vials
EU/1/20/1528/018

Multidose vials
EU/1/20/1528/019 10 multidose vials
EU/1/20/1528/020 195 multidose vials

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

COMIRNATY Omicron XBB.1.5 30 mcg injection
COVID-19 mRNA Vaccine
raxtozinameran
IM

2. METHOD OF ADMINISTRATION

Do not dilute

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Single dose vials
1 dose

Multidose vials
6 doses 30 mcg

6. OTHER

Multidose vials
Discard time:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

COMIRNATY Omicron XBB.1.5 10 micrograms/dose concentrate for dispersion for injection
children 5 to 11 years
COVID-19 mRNA Vaccine
raxtozinameran

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After dilution, each vial contains 10 doses of 0.2 mL.
One dose contains 10 micrograms raxtozinameran.

3. LIST OF EXCIPIENTS

Excipients: ALC-0315, ALC-0159, DSPC, cholesterol, trometamol, trometamol hydrochloride, sucrose, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for dispersion for injection
10 multidose vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use after dilution.
Read the package leaflet before use.



Scan for more information.
www.comirnatyglobal.com

Before use, dilute each vial with 1.3 mL sodium chloride 9 mg/mL (0.9%) solution for injection.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (at -90 °C to -60 °C)
Expiry date at 2 °C to 8 °C:
(Maximum 10 weeks. Cross out former expiry date.)

9. SPECIAL STORAGE CONDITIONS

Store at 2 °C to 8 °C after receipt. Do not refreeze.
Store in the original package in order to protect from light.
After dilution, store at 2 °C to 30 °C and use within 12 hours.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1528/021

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

COMIRNATY Omicron XBB.1.5 10 mcg sterile concentrate
COVID-19 mRNA Vaccine
raxtozinameran
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 doses 10 mcg after dilution

6. OTHER

Discard time:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

COMIRNATY Omicron XBB.1.5 10 micrograms/dose dispersion for injection
children 5 to 11 years
COVID-19 mRNA Vaccine
raxtozinameran

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One dose contains 10 micrograms raxtozinameran.

Single dose vials

Each vial contains 1 dose of 0.3 mL.

Multidose vials

Each vial contains 6 doses of 0.3 mL.

3. LIST OF EXCIPIENTS

Excipients: ALC-0315, ALC-0159, DSPC, cholesterol, trometamol, trometamol hydrochloride, sucrose, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for injection

Single dose vials

10 single dose vials

Multidose vials

10 multidose vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use.
Do not dilute prior to use.
Read the package leaflet before use.



Scan for more information.
www.comirnatyglobal.com

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (at -90 °C to -60 °C)
Expiry date at 2 °C to 8 °C:
(Maximum 10 weeks. Cross out former expiry date.)

9. SPECIAL STORAGE CONDITIONS

Store at 2 °C to 8 °C after receipt. Do not refreeze.
Store in the original package in order to protect from light.

Multidose vials

After first puncture, store at 2 °C to 30 °C and use within 12 hours.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

12. MARKETING AUTHORISATION NUMBER(S)

Single dose vials
EU/1/20/1528/022

Multidose vials
EU/1/20/1528/023

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

COMIRNATY Omicron XBB.1.5 10 mcg injection
COVID-19 mRNA Vaccine
raxtozinameran
IM

2. METHOD OF ADMINISTRATION

Do not dilute

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Single dose vials
1 dose

Multidose vials
6 doses 10 mcg

6. OTHER

Multidose vials
Discard time:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

COMIRNATY Omicron XBB.1.5 3 micrograms/dose concentrate for dispersion for injection
children 6 months to 4 years
COVID-19 mRNA Vaccine
raxtozinameran

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After dilution, each vial contains 10 doses of 0.2 mL.
One dose contains 3 micrograms raxtozinameran.

3. LIST OF EXCIPIENTS

Excipients: ALC-0315, ALC-0159, DSPC, cholesterol, trometamol, trometamol hydrochloride, sucrose, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for dispersion for injection
10 multidose vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use after dilution.
Read the package leaflet before use.



Scan for more information.
www.comirnatyglobal.com

Before use, dilute each vial with 2.2 mL sodium chloride 9 mg/mL (0.9%) solution for injection.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (at -90 °C to -60 °C)
Expiry date at 2 °C to 8 °C:
(Maximum 10 weeks. Cross out former expiry date.)

9. SPECIAL STORAGE CONDITIONS

Store at 2 °C to 8 °C after receipt. Do not refreeze.
Store in the original package in order to protect from light.
After dilution, store at 2 °C to 30 °C and use within 12 hours.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1528/024

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

COMIRNATY Omicron XBB.1.5 3 mcg sterile concentrate
COVID-19 mRNA Vaccine
raxtozinameran
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 doses 3 mcg after dilution

6. OTHER

Discard time:

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Comirnaty 30 micrograms/dose concentrate for dispersion for injection Adults and adolescents from 12 years COVID-19 mRNA Vaccine tozinameran

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you receive this vaccine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Comirnaty is and what it is used for
2. What you need to know before you receive Comirnaty
3. How Comirnaty is given
4. Possible side effects
5. How to store Comirnaty
6. Contents of the pack and other information

1. What Comirnaty is and what it is used for

Comirnaty is a vaccine used for preventing COVID-19 caused by SARS-CoV-2.

Comirnaty 30 micrograms/dose concentrate for dispersion for injection is given to adults and adolescents from 12 years of age and older.

The vaccine causes the immune system (the body's natural defences) to produce antibodies and blood cells that work against the virus, so giving protection against COVID-19.

As Comirnaty does not contain the virus to produce immunity, it cannot give you COVID-19.

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

2. What you need to know before you receive Comirnaty

Comirnaty should not be given

- if you are allergic to the active substance or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions

Talk to your doctor, pharmacist or nurse before you are given the vaccine if:

- you have ever had a severe allergic reaction or breathing problems after any other vaccine injection or after you were given this vaccine in the past.
- you are feeling nervous about the vaccination process or have ever fainted following any needle injection.
- you have a severe illness or infection with high fever. However, you can have your vaccination if you have a mild fever or upper airway infection like a cold.

- you have a bleeding problem, you bruise easily or you use a medicine to prevent blood-clots.
- you have a weakened immune system, because of a disease such as HIV infection or a medicine such as corticosteroid that affects your immune system.

There is an increased risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) after vaccination with Comirnaty (see section 4). 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. The risk of myocarditis and pericarditis seems lower in children ages 5 to 11 years compared with ages 12 to 17 years. Most cases of myocarditis and pericarditis recover. Some cases required intensive care support and fatal cases have been seen. Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

As with any vaccine, Comirnaty may not fully protect all those who receive it and it is not known how long you will be protected.

The efficacy of Comirnaty may be lower in people who are immunocompromised. If you are immunocompromised, you may receive additional doses of Comirnaty. In these cases, you should continue to maintain physical precautions to help prevent COVID-19. In addition, your close contacts should be vaccinated as appropriate. Discuss appropriate individual recommendations with your doctor.

Children

Comirnaty 30 micrograms/dose concentrate for dispersion for injection is not recommended for children aged under 12 years.

There are paediatric formulations available for infants aged 6 months and above and children below 12 years of age. For details, please refer to the Package Leaflet for other formulations.

The vaccine is not recommended for infants aged under 6 months.

Other medicines and Comirnaty

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines or have recently received any other vaccine.

Pregnancy and breast-feeding

If you are pregnant or think you may be pregnant, tell your doctor, nurse or pharmacist before you receive this vaccine.

Comirnaty can be used during pregnancy. A large amount of information from pregnant women vaccinated with Comirnaty during the second and third trimester have not shown negative effects on the pregnancy or the newborn baby. While information on effects on pregnancy or the newborn baby after vaccination during the first trimester is limited, no change to the risk for miscarriage has been seen.

Comirnaty can be given during breast-feeding.

Driving and using machines

Some of the effects of vaccination mentioned in section 4 (Possible side effects) may temporarily affect your ability to drive or use machines. Wait until these effects have worn off before you drive or use machines.

Comirnaty contains potassium and sodium

This vaccine contains less than 1 mmol potassium (39 mg) per dose, that is to say essentially 'potassium-free'.

This vaccine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

3. How Comirnaty is given

Comirnaty is given after dilution as an injection of 0.3 mL into a muscle of your upper arm.

You will receive 1 injection, regardless whether you have received a COVID-19 vaccine before.

If you were previously vaccinated with a COVID-19 vaccine, you should not receive a dose of Comirnaty until at least 3 months after the most recent dose.

If you are immunocompromised, you may receive additional doses of Comirnaty.

If you have any further questions on the use of Comirnaty, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all vaccines, Comirnaty can cause side effects, although not everybody gets them.

Very common side effects: may affect more than 1 in 10 people

- injection site: pain, swelling
- tiredness, headache
- muscle pain, joint pain
- chills, fever
- diarrhoea

Some of these side effects were slightly more frequent in adolescents 12 to 15 years than in adults.

Common side effects: may affect up to 1 in 10 people

- injection site redness
- nausea, vomiting
- enlarged lymph nodes (more frequently observed after a booster dose)

Uncommon side effects: may affect up to 1 in 100 people

- feeling unwell, feeling weak or lack of energy/sleepy
- arm pain
- insomnia
- injection site itching
- allergic reactions such as rash or itching
- decreased appetite
- dizziness
- excessive sweating, night sweats

Rare side effects: may affect up to 1 in 1 000 people

- temporary one sided facial drooping
- allergic reactions such as hives or swelling of the face

Very rare side effects: may affect up to 1 in 10 000 people

- inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain

Not known (cannot be estimated from the available data)

- severe allergic reaction
- extensive swelling of the vaccinated limb
- swelling of the face (swelling of the face may occur in patients who have had facial dermatological fillers)
- a skin reaction that causes red spots or patches on the skin, that may look like a target or “bulls-eye” with a dark red centre surrounded by paler red rings (erythema multiforme)
- unusual feeling in the skin, such as tingling or a crawling feeling (paraesthesia)
- decreased feeling or sensitivity, especially in the skin (hypoesthesia)
- heavy menstrual bleeding (most cases appeared to be non-serious and temporary in nature)

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system](#) listed in [Appendix V](#) and include batch/Lot number if available. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Comirnaty

Keep this medicine out of the sight and reach of children.

The following information about storage, expiry and use and handling is intended for healthcare professionals.

Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.

Store in freezer at -90 °C to -60 °C. Unopened vials may be stored and transported at -25 °C to -15 °C for a single period of up to 2 weeks and can be returned to -90 °C to -60 °C; not exceeding the printed expiry date (EXP).

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

When stored frozen at -90 °C to -60 °C, 195-vial packs of the vaccine can be thawed at 2 °C to 8 °C for 3 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Transfers of frozen vials stored at ultra-low temperature (< -60 °C)

- Closed-lid vial trays containing 195 vials removed from ultra-low temperature frozen storage (< -60 °C) may be at temperatures up to 25 °C for up to 5 minutes.
- Open-lid vial trays, or vial trays containing less than 195 vials, removed from ultra-low temperature frozen storage (< -60 °C) may be at temperatures up to 25 °C for up to 3 minutes.
- After vial trays are returned to frozen storage following temperature exposure up to 25 °C, they must remain in frozen storage for at least 2 hours before they can be removed again.

Transfers of frozen vials stored at -25 °C to -15 °C

- Closed-lid vial trays containing 195 vials removed from frozen storage (-25 °C to -15 °C) may be at temperatures up to 25 °C for up to 3 minutes.
- Open-lid vial trays, or vial trays containing less than 195 vials, removed from frozen storage (-25 °C to -15 °C) may be at temperatures up to 25 °C for up to 1 minute.

Once a vial is removed from the vial tray, it should be thawed for use.

After thawing, the vaccine should be diluted and used immediately. However, in-use stability data have demonstrated that once removed from freezer, the undiluted vaccine can be stored for up to 1 month at 2 °C to 8 °C; not exceeding the printed expiry date (EXP). Within the 1-month shelf life at

2 °C to 8 °C, up to 48 hours may be used for transportation. Prior to use, the unopened vaccine can be stored for up to 2 hours at temperatures up to 30 °C.

Thawed vials can be handled in room light conditions.

After dilution, store and transport the vaccine at 2 °C to 30 °C and use within 6 hours. Discard any unused vaccine.

Once removed from the freezer and diluted, the vials should be marked with the new discard date and time. Once thawed, the vaccine cannot be re-frozen.

Do not use this vaccine if you notice particulates in the dilution or discolouration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Comirnaty contains

- The active substance of COVID-19 mRNA Vaccine (nucleoside modified) is called tozinameran. After dilution, the vial contains 6 doses of 0.3 mL with 30 micrograms tozinameran each.
- The other ingredients are:
 - ((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
 - potassium chloride
 - potassium dihydrogen phosphate
 - sodium chloride
 - disodium phosphate dihydrate
 - sucrose
 - water for injections
 - sodium hydroxide (for pH adjustment)
 - hydrochloric acid (for pH adjustment)

What Comirnaty looks like and contents of the pack

The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9) provided in a multidose vial of 6 doses in a 2 mL clear vial (type I glass), with a rubber stopper and a purple flip-off plastic cap with aluminium seal.

Pack size: 195 vials

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- **Portugal:** Laboratórios Pfizer, Lda., Tel: +351 21 423 5500
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- **Slovenija:** Pfizer Luxembourg SARL, Pfizer, podružnica za svetovanje s področja farmacevtske dejavnosti, Ljubljana, Tel.: +386 (0) 1 52 11 400
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- **Sverige:** Pfizer AB, Tel: +46 (0)8 550 520 00
- **United Kingdom (Northern Ireland):** Pfizer Limited, Tel: +44 (0) 1304 616161

This leaflet was last revised in

Scan the code with a mobile device to get the package leaflet in different languages.



URL: www.comirnatyglobal.com

Detailed information on this medicine is available on the European Medicines Agency website:
<http://www.ema.europa.eu>.

The following information is intended for healthcare professionals only:

Administer Comirnaty intramuscularly after dilution as a single dose of 0.3 mL regardless of prior COVID-19 vaccination status.

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

Additional doses may be given to individuals who are severely immunocompromised.

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.

Handling instructions prior to use

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

- **Verify** that the vial has a **purple plastic cap** and the product **name is Comirnaty 30 micrograms/dose concentrate for dispersion for injection** (12 years and older).
- If the vial has another product name on the label, please make reference to the Summary of Product Characteristics for that formulation.
- The vial is stored frozen and must be thawed prior to dilution. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 195-vial pack may take 3 hours to thaw. Alternatively, frozen vials may also be thawed for 30 minutes at temperatures up to 30 °C for immediate use.
- The unopened vial can be **stored for up to 1 month at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP). Within the 1-month shelf life at 2 °C to 8 °C, up to 48 hours may be used for transportation.
- Allow the thawed vial to come to room temperature. Prior to use, the unopened vial can be stored for up to 2 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Dilution

- Gently invert the vial 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 **1.8 mL of 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 1.8 mL air into the empty diluent syringe.
- Gently invert the diluted dispersion 10 times. Do not shake.
- The diluted vaccine should present as an off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discolouration are present.
- The diluted vials should be marked with the appropriate **discard date and time**.
- **After dilution**, store at 2 °C to 30 °C and use within **6 hours**, including any transportation time.
- 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 2.25 mL from which 6 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.
Low dead-volume syringes and/or needles should be used in order to extract 6 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial.
- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
- Discard any unused vaccine within 6 hours after dilution.

Disposal

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

Package leaflet: Information for the user

Comirnaty 30 micrograms/dose dispersion for injection Adults and adolescents from 12 years COVID-19 mRNA Vaccine tozinameran

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you receive this vaccine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Comirnaty is and what it is used for
2. What you need to know before you receive Comirnaty
3. How Comirnaty is given
4. Possible side effects
5. How to store Comirnaty
6. Contents of the pack and other information

1. What Comirnaty is and what it is used for

Comirnaty is a vaccine used for preventing COVID-19 caused by SARS-CoV-2.

Comirnaty 30 micrograms/dose dispersion for injection is given to adults and adolescents from 12 years of age and older.

The vaccine causes the immune system (the body's natural defences) to produce antibodies and blood cells that work against the virus, so giving protection against COVID-19.

As Comirnaty does not contain the virus to produce immunity, it cannot give you COVID-19.

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

2. What you need to know before you receive Comirnaty

Comirnaty should not be given

- if you are allergic to the active substance or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions

Talk to your doctor, pharmacist or nurse before you are given the vaccine if:

- you have ever had a severe allergic reaction or breathing problems after any other vaccine injection or after you were given this vaccine in the past.
- you are feeling nervous about the vaccination process or have ever fainted following any needle injection.
- you have a severe illness or infection with high fever. However, you can have your vaccination if you have a mild fever or upper airway infection like a cold.

- you have a bleeding problem, you bruise easily or you use a medicine to prevent blood-clots.
- you have a weakened immune system, because of a disease such as HIV infection or a medicine such as corticosteroid that affects your immune system.

There is an increased risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) after vaccination with Comirnaty (see section 4). 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. The risk of myocarditis and pericarditis seems lower in children ages 5 to 11 years compared with ages 12 to 17 years. Most cases of myocarditis and pericarditis recover. Some cases required intensive care support and fatal cases have been seen. Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

As with any vaccine, Comirnaty may not fully protect all those who receive it and it is not known how long you will be protected.

The efficacy of Comirnaty may be lower in people who are immunocompromised. If you are immunocompromised, you may receive additional doses of Comirnaty. In these cases, you should continue to maintain physical precautions to help prevent COVID-19. In addition, your close contacts should be vaccinated as appropriate. Discuss appropriate individual recommendations with your doctor.

Children

Comirnaty 30 micrograms/dose dispersion for injection is not recommended for children aged under 12 years.

There are paediatric formulations available for infants aged 6 months and above and children below 12 years of age. For details, please refer to the Package Leaflet for other formulations.

The vaccine is not recommended for infants aged under 6 months.

Other medicines and Comirnaty

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines or have recently received any other vaccine.

Pregnancy and breast-feeding

If you are pregnant or think you may be pregnant, tell your doctor, nurse or pharmacist before you receive this vaccine.

Comirnaty can be used during pregnancy. A large amount of information from pregnant women vaccinated with Comirnaty during the second and third trimester have not shown negative effects on the pregnancy or the newborn baby. While information on effects on pregnancy or the newborn baby after vaccination during the first trimester is limited, no change to the risk for miscarriage has been seen.

Comirnaty can be given during breast-feeding.

Driving and using machines

Some of the effects of vaccination mentioned in section 4 (Possible side effects) may temporarily affect your ability to drive or use machines. Wait until these effects have worn off before you drive or use machines.

3. How Comirnaty is given

Comirnaty is given as an injection of 0.3 mL into a muscle of your upper arm.

You will receive 1 injection, regardless whether you have received a COVID-19 vaccine before.

If you were previously vaccinated with a COVID-19 vaccine, you should not receive a dose of Comirnaty until at least 3 months after the most recent dose.

If you are immunocompromised, you may receive additional doses of Comirnaty.

If you have any further questions on the use of Comirnaty, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all vaccines, Comirnaty can cause side effects, although not everybody gets them.

Very common side effects: may affect more than 1 in 10 people

- injection site: pain, swelling
- tiredness, headache
- muscle pain, joint pain
- chills, fever
- diarrhoea

Some of these side effects were slightly more frequent in adolescents 12 to 15 years than in adults.

Common side effects: may affect up to 1 in 10 people

- injection site redness
- nausea, vomiting
- enlarged lymph nodes (more frequently observed after a booster dose)

Uncommon side effects: may affect up to 1 in 100 people

- feeling unwell, feeling weak or lack of energy/sleepy
- arm pain
- insomnia
- injection site itching
- allergic reactions such as rash or itching
- decreased appetite
- dizziness
- excessive sweating, night sweats

Rare side effects: may affect up to 1 in 1 000 people

- temporary one sided facial drooping
- allergic reactions such as hives or swelling of the face

Very rare side effects: may affect up to 1 in 10 000 people

- inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain

Not known (cannot be estimated from the available data)

- severe allergic reaction
- extensive swelling of the vaccinated limb
- swelling of the face (swelling of the face may occur in patients who have had facial dermatological fillers)
- a skin reaction that causes red spots or patches on the skin, that may look like a target or “bulls-eye” with a dark red centre surrounded by paler red rings (erythema multiforme)

- unusual feeling in the skin, such as tingling or a crawling feeling (paraesthesia)
- decreased feeling or sensitivity, especially in the skin (hypoesthesia)
- heavy menstrual bleeding (most cases appeared to be non-serious and temporary in nature)

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system](#) listed in [Appendix V](#) and include batch/Lot number if available. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Comirnaty

Keep this medicine out of the sight and reach of children.

The following information about storage, expiry and use and handling is intended for healthcare professionals.

Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.

Store in freezer at -90 °C to -60 °C.

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

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.

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 or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Multidose vials: 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 6 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed vials: Once removed from the freezer, the unopened vial may be stored and transported refrigerated at 2 °C to 8 °C for up to 10 weeks; not exceeding the printed expiry date (EXP). The outer carton should be marked with the new discard date at 2 °C to 8 °C. Once thawed, the vaccine cannot be re-frozen.

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

Thawed vials can be handled in room light conditions.

Opened vials: After first puncture, store the vaccine at 2 °C to 30 °C and use within 12 hours, which includes up to 6 hours transportation time. Discard any unused vaccine.

Do not use this vaccine if you notice particulates or discolouration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Comirnaty contains

- The active substance of COVID-19 mRNA Vaccine (nucleoside modified) is called tozinameran.
 - A single dose vial contains 1 dose of 0.3 mL with 30 micrograms tozinameran each.
 - A multidose vial contains 6 doses of 0.3 mL with 30 micrograms tozinameran each.
- The other ingredients are:
 - ((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

What Comirnaty looks like and contents of the pack

The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9) provided in either:

- A single dose vial of 1 dose in a 2 mL clear vial (type I glass), with a rubber stopper and a grey flip-off plastic cap with aluminium seal; or
- A multidose vial of 6 doses in a 2 mL clear vial (type I glass), with a rubber stopper and a grey flip-off plastic cap with aluminium seal.

Single dose vial pack size: 10 vials

Multidose vial pack sizes: 10 vials or 195 vials

Not all pack sizes may be marketed.

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- **Malta:** Vivian Corporation Ltd., Tel: +35621 344610
- **Norge:** Pfizer AS, Tlf: +47 67 526 100
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- **Slovenija:** Pfizer Luxembourg SARL, Pfizer, podružnica za svetovanje s področja farmacevtske dejavnosti, Ljubljana, Tel.: +386 (0) 1 52 11 400
- **Slovenská republika:** Pfizer Luxembourg SARL, organizačná zložka, Tel: +421 2 3355 5500
- **Suomi/Finland:** Pfizer Oy, Puh/Tel: +358 (0)9 430 040
- **Sverige:** Pfizer AB, Tel: +46 (0)8 550 520 00
- **United Kingdom (Northern Ireland):** Pfizer Limited, Tel: +44 (0) 1304 616161

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URL: www.comirnatyglobal.com

Detailed information on this medicine is available on the European Medicines Agency website:
<http://www.ema.europa.eu>

The following information is intended for healthcare professionals only:

Administer Comirnaty intramuscularly as a single dose of 0.3 mL regardless of prior COVID-19 vaccination status.

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

Additional doses may be given to individuals who are severely immunocompromised.

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.

Handling instructions prior to use

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

- **Verify** that the vial has a **grey plastic cap** and the product **name is Comirnaty 30 micrograms/dose dispersion for injection** (12 years and older).
- If the vial has another product name on the label, please make reference to the Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw. Ensure vials are completely thawed prior to use.
 - 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).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C. Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Preparation of 0.3 mL doses

- Gently mix by inverting vials 10 times prior to use. Do not shake.
- Prior to mixing, the thawed dispersion may contain white to off-white opaque amorphous particles.
- After mixing, the vaccine should present as a white to off-white 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.

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 vial. Discard any unused vaccine 12 hours after first puncture.

Disposal

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

Package leaflet: Information for the user

Comirnaty 10 micrograms/dose concentrate for dispersion for injection Children 5 to 11 years COVID-19 mRNA Vaccine tozinameran

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects your child may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before your child receives this vaccine because it contains important information for your child.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your child's doctor, pharmacist or nurse.
- If your child gets any side effects, talk to your child's doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Comirnaty is and what it is used for
2. What you need to know before your child receives Comirnaty
3. How Comirnaty is given
4. Possible side effects
5. How to store Comirnaty
6. Contents of the pack and other information

1. What Comirnaty is and what it is used for

Comirnaty is a vaccine used for preventing COVID-19 caused by SARS-CoV-2.

Comirnaty 10 micrograms/dose concentrate for dispersion for injection is given to children from 5 to 11 years of age.

The vaccine causes the immune system (the body's natural defences) to produce antibodies and blood cells that work against the virus, so giving protection against COVID-19.

As Comirnaty does not contain the virus to produce immunity, it cannot give your child COVID-19.

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

2. What you need to know before your child receives Comirnaty

Comirnaty should not be given

- if your child is allergic to the active substance or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions

Talk to your child's doctor, pharmacist or nurse before your child is given the vaccine if your child:

- has ever had a severe allergic reaction or breathing problems after any other vaccine injection or after having been given this vaccine in the past.
- is feeling nervous about the vaccination process or has ever fainted following any needle injection.
- has a severe illness or infection with high fever. However, your child can have the vaccination if he/she has a mild fever or upper airway infection like a cold.

- has a bleeding problem, bruises easily or uses a medicine to prevent blood-clots.
- has a weakened immune system, because of a disease such as HIV infection or a medicine such as corticosteroid that affects the immune system.

There is an increased risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) after vaccination with Comirnaty (see section 4). 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. The risk of myocarditis and pericarditis seems lower in children ages 5 to 11 years compared with ages 12 to 17 years. Most cases of myocarditis and pericarditis recover. Some cases required intensive care support and fatal cases have been seen. Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

As with any vaccine, Comirnaty may not fully protect all those who receive it and it is not known how long your child will be protected.

The efficacy of Comirnaty may be lower in people who are immunocompromised. If your child is immunocompromised, he/she may receive additional doses of Comirnaty. In these cases, your child should continue to maintain physical precautions to help prevent COVID-19. In addition, your child's close contacts should be vaccinated as appropriate. Discuss appropriate individual recommendations with your child's doctor.

Children

Comirnaty 10 micrograms/dose concentrate for dispersion for injection is not recommended for children aged under 5 years.

There are paediatric formulations available for infants and children aged 6 months to 4 years. For details, please refer to the Package Leaflet for other formulations.

The vaccine is not recommended for infants aged under 6 months.

Other medicines and Comirnaty

Tell your child's doctor or pharmacist if your child is using, has recently used or might use any other medicines or has recently received any other vaccine.

Pregnancy and breast-feeding

If your child is pregnant, tell your child's doctor, nurse or pharmacist before your child receives this vaccine.

Comirnaty can be used during pregnancy. A large amount of information from pregnant women vaccinated with Comirnaty during the second and third trimester have not shown negative effects on the pregnancy or the newborn baby. While information on effects on pregnancy or the newborn baby after vaccination during the first trimester is limited, no change to the risk for miscarriage has been seen.

Comirnaty can be given during breast-feeding.

Driving and using machines

Some of the effects of vaccination mentioned in section 4 (Possible side effects) may temporarily affect your child's ability to use machines or undertake activities such as cycling. Wait until these effects have worn off before resuming activities that require your child's full attention.

3. How Comirnaty is given

Comirnaty is given after dilution as an injection of 0.2 mL into a muscle of your child's upper arm.

Your child will receive 1 injection, regardless whether he/she has received a COVID-19 vaccine before.

If your child was previously vaccinated with a COVID-19 vaccine, he/she should not receive a dose of Comirnaty until at least 3 months after the most recent dose.

If your child is immunocompromised, he/she may receive additional doses of Comirnaty.

If you have any further questions on the use of Comirnaty, ask your child's doctor, pharmacist or nurse.

4. Possible side effects

Like all vaccines, Comirnaty can cause side effects, although not everybody gets them.

Very common side effects: may affect more than 1 in 10 people

- injection site: pain, swelling
- tiredness, headache
- muscle pain, joint pain
- chills, fever
- diarrhoea

Common side effects: may affect up to 1 in 10 people

- nausea, vomiting
- injection site redness ('very common' in 5 to 11 years of age)
- enlarged lymph nodes (more frequently observed after a booster dose)

Uncommon side effects: may affect up to 1 in 100 people

- feeling unwell, feeling weak or lack of energy/sleepy
- arm pain
- insomnia
- injection site itching
- allergic reactions such as rash or itching
- decreased appetite
- dizziness
- excessive sweating, night sweats

Rare side effects: may affect up to 1 in 1 000 people

- temporary one sided facial drooping
- allergic reactions such as hives or swelling of the face

Very rare side effects: may affect up to 1 in 10 000 people

- inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain

Not known (cannot be estimated from the available data)

- severe allergic reaction
- extensive swelling of the vaccinated limb
- swelling of the face (swelling of the face may occur in patients who have had facial dermatological fillers)

- a skin reaction that causes red spots or patches on the skin, that may look like a target or “bulls-eye” with a dark red centre surrounded by paler red rings (erythema multiforme)
- unusual feeling in the skin, such as tingling or a crawling feeling (paraesthesia)
- decreased feeling or sensitivity, especially in the skin (hypoaesthesia)
- heavy menstrual bleeding (most cases appeared to be non-serious and temporary in nature)

Reporting of side effects

If your child gets any side effects, talk to your child’s doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system](#) listed in [Appendix V](#) and include batch/Lot number if available. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Comirnaty

Keep this medicine out of the sight and reach of children.

The following information about storage, expiry and use and handling is intended for healthcare professionals.

Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.

Store in freezer at -90 °C to -60 °C.

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

The vaccine will be received frozen at -90 °C to -60 °C. Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

When stored frozen at -90 °C to -60 °C, 10-vial packs of the vaccine can be thawed at 2 °C to 8 °C for 4 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Once removed from the freezer, the unopened vial may be stored and transported refrigerated at 2 °C to 8 °C for up to 10 weeks; not exceeding the printed expiry date (EXP). The outer carton should be marked with the new discard date at 2 °C to 8 °C. Once thawed, the vaccine cannot be re-frozen.

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

Thawed vials can be handled in room light conditions.

After dilution, store the vaccine at 2 °C to 30 °C and use within 12 hours, which includes up to 6 hours transportation time. Discard any unused vaccine.

Do not use this vaccine if you notice particulates in the dilution or discolouration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Comirnaty contains

- The active substance of COVID-19 mRNA Vaccine (nucleoside modified) is called tozinameran. After dilution, the vial contains 10 doses of 0.2 mL with 10 micrograms tozinameran each.
- The other ingredients are:
 - ((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

What Comirnaty looks like and contents of the pack

The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9) provided in a multidose vial of 10 doses in a 2 mL clear vial (type I glass), with a rubber stopper and an orange flip-off plastic cap with aluminium seal.

Pack sizes: 10 vials or 195 vials
Not all pack sizes may be marketed.

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This leaflet was last revised in

Scan the code with a mobile device to get the package leaflet in different languages.



URL: www.comirnatyglobal.com

Detailed information on this medicine is available on the European Medicines Agency website:
<http://www.ema.europa.eu>

The following information is intended for healthcare professionals only:

Administer Comirnaty intramuscularly after dilution as a single dose of 0.2 mL regardless of prior COVID-19 vaccination status.

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

Additional doses may be given to individuals who are severely immunocompromised.

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.

Handling instructions prior to use

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

- Verify that the vial has an **orange plastic cap** and the product **name is Comirnaty 10 micrograms/dose concentrate for dispersion for injection** (children 5 to 11 years).
- If the vial has another product name on the label, please make reference to the Summary of Product Characteristics 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 4 hours to thaw. Ensure vials are completely thawed prior to use.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Dilution

- 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 **1.3 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 1.3 mL air into the empty diluent syringe.
- Gently invert the diluted dispersion 10 times. Do not shake.
- The diluted vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discolouration are present.
- The diluted vials should be marked with the appropriate **discard date and time**.
- **After dilution**, store at 2 °C to 30 °C and use within **12 hours**.
- Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.

Preparation of 0.2 mL doses

- 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 for children aged 5 to 11 years.
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 12 hours after dilution.

Disposal

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

Package leaflet: Information for the user

Comirnaty 3 micrograms/dose concentrate for dispersion for injection Infants and children 6 months to 4 years COVID-19 mRNA Vaccine tozinameran

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects your child may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before your child receives this vaccine because it contains important information for your child.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your child's doctor, pharmacist or nurse.
- If your child gets any side effects, talk to your child's doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Comirnaty is and what it is used for
2. What you need to know before your child receives Comirnaty
3. How Comirnaty is given
4. Possible side effects
5. How to store Comirnaty
6. Contents of the pack and other information

1. What Comirnaty is and what it is used for

Comirnaty is a vaccine used for preventing COVID-19 caused by SARS-CoV-2.

Comirnaty 3 micrograms/dose concentrate for dispersion for injection is given to infants and children from 6 months to 4 years of age.

The vaccine causes the immune system (the body's natural defences) to produce antibodies and blood cells that work against the virus, so giving protection against COVID-19.

As Comirnaty does not contain the virus to produce immunity, it cannot give your child COVID-19.

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

2. What you need to know before your child receives Comirnaty

Comirnaty should not be given

- if your child is allergic to the active substance or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions

Talk to your child's doctor, pharmacist or nurse before your child is given the vaccine if your child:

- has ever had a severe allergic reaction or breathing problems after any other vaccine injection or after having been given this vaccine in the past.
- is feeling nervous about the vaccination process or has ever fainted following any needle injection.
- has a severe illness or infection with high fever. However, your child can have the vaccination if he/she has a mild fever or upper airway infection like a cold.

- has a bleeding problem, bruises easily or uses a medicine to prevent blood-clots.
- has a weakened immune system, because of a disease such as HIV infection or a medicine such as corticosteroid that affects the immune system.

There is an increased risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) after vaccination with Comirnaty (see section 4). 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. The risk of myocarditis and pericarditis seems lower in children ages 5 to 11 years compared with ages 12 to 17 years. Most cases of myocarditis and pericarditis recover. Some cases required intensive care support and fatal cases have been seen. Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

As with any vaccine, Comirnaty may not fully protect all those who receive it and it is not known how long your child will be protected.

The efficacy of Comirnaty may be lower in people who are immunocompromised. If your child is immunocompromised, he/she may receive additional doses of Comirnaty. In these cases, your child should continue to maintain physical precautions to help prevent COVID-19. In addition, your child's close contacts should be vaccinated as appropriate. Discuss appropriate individual recommendations with your child's doctor.

Children

Comirnaty 3 micrograms/dose concentrate for dispersion for injection is not recommended for children aged 5 years to 11 years.

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

The vaccine is not recommended for infants aged under 6 months.

Other medicines and Comirnaty

Tell your child's doctor or pharmacist if your child is using, has recently used or might use any other medicines or has recently received any other vaccine.

Pregnancy and breast-feeding

Comirnaty 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 Package Leaflet for those formulations.

Driving and using machines

Some of the effects of vaccination mentioned in section 4 (Possible side effects) may temporarily affect your child's ability to use machines or undertake activities such as cycling. Wait until these effects have worn off before resuming activities that require your child's full attention.

3. How Comirnaty is given

If your infant is from 6 months to less than 12 months of age, he/she will be given Comirnaty after dilution as an injection of 0.2 mL into a muscle of the thigh. If your infant or child is 1 year of age or older, he/she will be given Comirnaty after dilution as an injection of 0.2 mL into a muscle of the thigh or into a muscle of the upper arm.

If your child has not completed a COVID-19 primary vaccination course or has not been infected by COVID-19 in the past, your child will receive a maximum of 3 injections (the total number of doses required as primary course). It is recommended to receive the second dose 3 weeks after the first dose followed by a third dose at least 8 weeks after the second dose to complete the primary course.

If your child has previously completed a COVID-19 primary vaccination course or has had COVID-19, your child will receive 1 injection. If your child was previously vaccinated with a COVID-19 vaccine, your child should not receive a dose of Comirnaty until at least 3 months after the most recent dose.

If your 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.

If your child is immunocompromised, he/she may receive additional doses of Comirnaty.

Interchangeability

Your child may receive either Comirnaty, Comirnaty Original/Omicron BA.4-5, or Comirnaty Omicron XBB.1.5 (or a combination) for the primary course. Your child should not receive more than the total number of doses needed as primary course. Your child should only be administered the primary course once.

If you have any further questions on the use of Comirnaty, ask your child's doctor, pharmacist or nurse.

4. Possible side effects

Like all vaccines, Comirnaty can cause side effects, although not everybody gets them.

Very common side effects: may affect more than 1 in 10 people

- irritability (6 months to < 2 years)
- injection site: pain/tenderness, swelling
- tiredness, headache
- drowsiness (6 months to < 2 years)
- muscle pain, joint pain
- chills, fever
- diarrhoea

Common side effects: may affect up to 1 in 10 people

- nausea, vomiting
- injection site redness ('very common' in 6 months to 11 years)
- enlarged lymph nodes (more frequently observed after a booster dose)

Uncommon side effects: may affect up to 1 in 100 people

- feeling unwell, feeling weak or lack of energy/sleepy
- arm pain
- insomnia
- injection site itching
- allergic reactions such as rash ('common' for 6 months to < 2 years) or itching
- decreased appetite ('very common' for 6 months to < 2 years)
- dizziness
- excessive sweating, night sweats

Rare side effects: may affect up to 1 in 1 000 people

- temporary one sided facial drooping
- allergic reactions such as hives or swelling of the face

Very rare side effects: may affect up to 1 in 10 000 people

- inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain

Not known (cannot be estimated from the available data)

- severe allergic reaction
- extensive swelling of the vaccinated limb
- swelling of the face (swelling of the face may occur in patients who have had facial dermatological fillers)
- a skin reaction that causes red spots or patches on the skin, that may look like a target or “bulls-eye” with a dark red centre surrounded by paler red rings (erythema multiforme)
- unusual feeling in the skin, such as tingling or a crawling feeling (paraesthesia)
- decreased feeling or sensitivity, especially in the skin (hypoesthesia)
- heavy menstrual bleeding (most cases appeared to be non-serious and temporary in nature)

Reporting of side effects

If your child gets any side effects, talk to your child’s doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via **the national reporting system** listed in [Appendix V](#) and include batch/Lot number if available. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Comirnaty

Keep this medicine out of the sight and reach of children.

The following information about storage, expiry and use and handling is intended for healthcare professionals.

Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.

Store in freezer at -90 °C to -60 °C.

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

The vaccine will be received frozen at -90 °C to -60 °C. Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

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

Once removed from the freezer, the unopened vial may be stored and transported refrigerated at 2 °C to 8 °C for up to 10 weeks; not exceeding the printed expiry date (EXP). The outer carton should be marked with the new discard date at 2 °C to 8 °C. Once thawed, the vaccine cannot be re-frozen.

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

Thawed vials can be handled in room light conditions.

After dilution, store the vaccine at 2 °C to 30 °C and use within 12 hours, which includes up to 6 hours transportation time. Discard any unused vaccine.

Do not use this vaccine if you notice particulates in the dilution or discolouration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Comirnaty contains

- The active substance of COVID-19 mRNA Vaccine (nucleoside modified) is called tozinameran. After dilution, the vial contains 10 doses of 0.2 mL with 3 micrograms tozinameran each.
- The other ingredients are:
 - ((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

What Comirnaty looks like and contents of the pack

The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9) provided in a multidose vial of 10 doses in a 2 mL clear vial (type I glass), with a rubber stopper and a maroon flip-off plastic cap with aluminium seal.

Pack size: 10 vials

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- **Slovenija:** Pfizer Luxembourg SARL, Pfizer, podružnica za svetovanje s področja farmacevtske dejavnosti, Ljubljana, Tel.: +386 (0) 1 52 11 400
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- **Suomi/Finland:** Pfizer Oy, Puh/Tel: +358 (0)9 430 040
- **Sverige:** Pfizer AB, Tel: +46 (0)8 550 520 00
- **United Kingdom (Northern Ireland):** Pfizer Limited, Tel: +44 (0) 1304 616161

This leaflet was last revised in

Scan the code with a mobile device to get the package leaflet in different languages.



URL: www.comirnatyglobal.com

Detailed information on this medicine is available on the European Medicines Agency website:
<http://www.ema.europa.eu>

The following information is intended for healthcare professionals only:

If the child has not completed a COVID-19 primary vaccination course or does not have a history of prior SARS-CoV-2 infection, administer Comirnaty intramuscularly after dilution as a primary course of maximum 3 doses (the total number of doses required as primary course) (0.2 mL each); the second dose administered 3 weeks after the first dose followed by a third dose at least 8 weeks after the second dose to complete the primary course.

If the child has completed a COVID-19 primary vaccination course or has a history of prior SARS-CoV-2 infection, administer Comirnaty intramuscularly after dilution a single dose of 0.2 mL. If the individual was previously vaccinated with a COVID-19 vaccine, the individual should receive a dose of Comirnaty at least 3 months after the most recent dose.

Additional doses may be given to individuals who are severely immunocompromised.

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.

Handling instructions prior to use

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

- **Verify** that the vial has a **maroon plastic cap** and the product **name is Comirnaty 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, please make reference to the Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 10-vial pack may take 2 hours to thaw. Ensure vials are completely thawed prior to use.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Dilution

- 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 **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 2.2 mL air into the empty diluent syringe.
- Gently invert the diluted dispersion 10 times. Do not shake.
- The diluted vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discolouration are present.
- The diluted vials should be marked with the appropriate **discard date and time**.
- **After dilution**, store at 2 °C to 30 °C and use within **12 hours**.
- Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.

Preparation of 0.2 mL doses

- 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 for infants and children aged 6 months to 4 years. **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 12 hours after dilution.

Disposal

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

Package leaflet: Information for the user

Comirnaty Original/Omicron BA.1 (15/15 micrograms)/dose dispersion for injection Adults and adolescents from 12 years COVID-19 mRNA Vaccine tozinameran/riltozinameran

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you receive this vaccine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Comirnaty Original/Omicron BA.1 is and what it is used for
2. What you need to know before you receive Comirnaty Original/Omicron BA.1
3. How Comirnaty Original/Omicron BA.1 is given
4. Possible side effects
5. How to store Comirnaty Original/Omicron BA.1
6. Contents of the pack and other information

1. What Comirnaty Original/Omicron BA.1 is and what it is used for

Comirnaty Original/Omicron BA.1 is a vaccine used for preventing COVID-19 caused by SARS-CoV-2. It is given to adults and adolescents from 12 years of age and older.

Comirnaty Original/Omicron BA.1 is only for individuals who have previously received at least a primary vaccination course against COVID-19.

The vaccine causes the immune system (the body's natural defences) to produce antibodies and blood cells that work against the virus, so giving protection against COVID-19.

As Comirnaty Original/Omicron BA.1 does not contain the virus to produce immunity, it cannot give you COVID-19.

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

2. What you need to know before you receive Comirnaty Original/Omicron BA.1

Comirnaty Original/Omicron BA.1 should not be given

- if you are allergic to the active substance or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions

Talk to your doctor, pharmacist or nurse before you are given the vaccine if:

- you have ever had a severe allergic reaction or breathing problems after any other vaccine injection or after you were given this vaccine in the past.
- you are feeling nervous about the vaccination process or have ever fainted following any needle injection.

- you have a severe illness or infection with high fever. However, you can have your vaccination if you have a mild fever or upper airway infection like a cold.
- you have a bleeding problem, you bruise easily or you use a medicine to prevent blood-clots.
- you have a weakened immune system, because of a disease such as HIV infection or a medicine such as corticosteroid that affects your immune system.

There is an increased risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) after vaccination with Comirnaty (see section 4). 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. The risk of myocarditis and pericarditis seems lower in children ages 5 to 11 years compared with ages 12 to 17 years. Most cases of myocarditis and pericarditis recover. Some cases required intensive care support and fatal cases have been seen. Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

As with any vaccine, Comirnaty Original/Omicron BA.1 may not fully protect all those who receive it and it is not known how long you will be protected.

The efficacy of Comirnaty Original/Omicron BA.1 may be lower in people who are immunocompromised. If you are immunocompromised, you may receive additional doses of Comirnaty Original/Omicron BA.1. In these cases, you should continue to maintain physical precautions to help prevent COVID-19. In addition, your close contacts should be vaccinated as appropriate. Discuss appropriate individual recommendations with your doctor.

Children

Comirnaty Original/Omicron BA.1 (15/15 micrograms)/dose dispersion for injection is not recommended for children aged under 12 years.

There are paediatric formulations available for infants aged 6 months and above and children below 12 years of age. For details, please refer to the Package Leaflet for other formulations.

The vaccine is not recommended for infants aged under 6 months.

Other medicines and Comirnaty Original/Omicron BA.1

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines or have recently received any other vaccine.

Pregnancy and breast-feeding

If you are pregnant or think you may be pregnant, tell your doctor, nurse or pharmacist before you receive this vaccine.

No data are available yet regarding the use of Comirnaty Original/Omicron BA.1 during pregnancy. However, a large amount of information from pregnant women vaccinated with the initially approved Comirnaty vaccine during the second and third trimester have not shown negative effects on the pregnancy or the newborn baby. While information on effects on pregnancy or the newborn baby after vaccination during the first trimester is limited, no change to the risk for miscarriage has been seen. Comirnaty Original/Omicron BA.1 can be used during pregnancy.

No data are available yet regarding the use of Comirnaty Original/Omicron BA.1 during breast-feeding. However, no effects on the breastfed newborn/infant are anticipated. 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 Original/Omicron BA.1 can be used while breast-feeding.

Driving and using machines

Some of the effects of vaccination mentioned in section 4 (Possible side effects) may temporarily affect your ability to drive or use machines. Wait until these effects have worn off before you drive or use machines.

3. How Comirnaty Original/Omicron BA.1 is given

Comirnaty Original/Omicron BA.1 is given as an injection of 0.3 mL into a muscle of your upper arm.

Comirnaty Original/Omicron BA.1 is only for individuals who have previously received at least a primary vaccination course against COVID-19.

Comirnaty Original/Omicron BA.1 may be given at least 3 months after the most recent dose of a COVID-19 vaccine.

Please check with your healthcare provider regarding eligibility for and timing of the booster dose.

If you are immunocompromised, you may receive additional doses of Comirnaty Original/Omicron BA.1.

For details on the primary vaccination course in individuals 12 years of age and older, please refer to the Package Leaflet for those formulations.

If you have any further questions on the use of Comirnaty Original/Omicron BA.1, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all vaccines, Comirnaty Original/Omicron BA.1 can cause side effects, although not everybody gets them.

Very common side effects: may affect more than 1 in 10 people

- injection site: pain, swelling
- tiredness, headache
- muscle pain, joint pain
- chills, fever
- diarrhoea

Some of these side effects were slightly more frequent in adolescents 12 to 15 years than in adults.

Common side effects: may affect up to 1 in 10 people

- injection site redness
- nausea, vomiting
- enlarged lymph nodes (more frequently observed after a booster dose)

Uncommon side effects: may affect up to 1 in 100 people

- feeling unwell, feeling weak or lack of energy/sleepy
- arm pain
- insomnia
- injection site itching
- allergic reactions such as rash or itching
- decreased appetite
- dizziness
- excessive sweating, night sweats

Rare side effects: may affect up to 1 in 1 000 people

- temporary one sided facial drooping
- allergic reactions such as hives or swelling of the face

Very rare side effects: may affect up to 1 in 10 000 people

- inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain

Not known (cannot be estimated from the available data)

- severe allergic reaction
- extensive swelling of the vaccinated limb
- swelling of the face (swelling of the face may occur in patients who have had facial dermatological fillers)
- a skin reaction that causes red spots or patches on the skin, that may look like a target or “bulls-eye” with a dark red centre surrounded by paler red rings (erythema multiforme)
- unusual feeling in the skin, such as tingling or a crawling feeling (paraesthesia)
- decreased feeling or sensitivity, especially in the skin (hypoesthesia)
- heavy menstrual bleeding (most cases appeared to be non-serious and temporary in nature)

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#) and include batch/Lot number if available. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Comirnaty Original/Omicron BA.1

Keep this medicine out of the sight and reach of children.

The following information about storage, expiry and use and handling is intended for healthcare professionals.

Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.

Store in freezer at -90 °C to -60 °C.

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

The vaccine will be received frozen at -90 °C to -60 °C. Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

When stored frozen at -90 °C to -60 °C, 10-vial packs of the vaccine can be thawed at 2 °C to 8 °C for 6 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Once removed from the freezer, the unopened vial may be stored and transported refrigerated at 2 °C to 8 °C for up to 10 weeks; not exceeding the printed expiry date (EXP). The outer carton should be marked with the new discard date at 2 °C to 8 °C. Once thawed, the vaccine cannot be re-frozen.

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

Thawed vials can be handled in room light conditions.

After first puncture, store the vaccine at 2 °C to 30 °C and use within 12 hours, which includes up to 6 hours transportation time. Discard any unused vaccine.

Do not use this vaccine if you notice particulates or discolouration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Comirnaty Original/Omicron BA.1 contains

- The active substances of COVID-19 mRNA Vaccine (nucleoside modified) are called tozinameran and riltozinameran. The vial contains 6 doses of 0.3 mL with 15 micrograms of tozinameran (Original) and 15 micrograms of riltozinameran (Omicron BA.1) per dose.
- The other ingredients are:
 - ((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

What Comirnaty Original/Omicron BA.1 looks like and contents of the pack

The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9) provided in a multidose vial of 6 doses in a 2 mL clear vial (type I glass), with a rubber stopper and a grey flip-off plastic cap with aluminium seal.

Pack sizes: 10 vials or 195 vials

Not all pack sizes may be marketed.

Marketing Authorisation Holder

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

Manufacturers

BioNTech Manufacturing GmbH
Kupferbergterrasse 17 - 19
55116 Mainz
Germany

Pfizer Manufacturing Belgium NV
Rijksweg 12
Puurs-Sint-Amands, 2870
Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

- **België/Belgique/Belgien, Luxembourg/Luxemburg:** Pfizer S.A./N.V., Tél/Tel: +32 (0)2 554 62 11
- **България:** Пфайзер Люксембург САРЛ, Клон, България, Тел: +359 2 970 4333
- **Česká republika:** Pfizer, spol. s r.o., Tel: +420 283 004 111
- **Danmark:** Pfizer ApS, Tlf: +45 44 201 100
- **Deutschland:** BioNTech Manufacturing GmbH, Tel: +49 6131 90840
- **Eesti:** Pfizer Luxembourg SARL Eesti filiaal, Tel: +372 666 7500
- **Ελλάδα:** Pfizer Ελλάς Α.Ε., Τηλ.: +30 210 6785 800
- **España:** Pfizer, S.L., Tel: +34914909900
- **France:** Pfizer, Tél +33 1 58 07 34 40
- **Hrvatska:** Pfizer Croatia d.o.o., Tel: +385 1 3908 777
- **Ireland:** Pfizer Healthcare Ireland, Tel: 1800 633 363 (toll free), +44 (0)1304 616161
- **Ísland:** Icepharma hf, Simi: +354 540 8000
- **Italia:** Pfizer S.r.l., Tel: +39 06 33 18 21
- **Κύπρος:** Pfizer Ελλάς Α.Ε. (Cyprus Branch), Τηλ: +357 22 817690
- **Latvija:** Pfizer Luxembourg SARL filiāle Latvijā, Tel.: +371 670 35 775
- **Lietuva:** Pfizer Luxembourg SARL filialas Lietuvoje, Tel. +370 52 51 4000
- **Magyarország:** Pfizer Kft, Tel: +36 1 488 3700
- **Malta:** Vivian Corporation Ltd., Tel: +35621 344610
- **Norge:** Pfizer AS, Tlf: +47 67 526 100
- **Nederland:** Pfizer BV, Tel: +31 (0)10 406 43 01
- **Österreich:** Pfizer Corporation Austria Ges.m.b.H, Tel: +43 (0)1 521 15-0
- **Polska:** Pfizer Polska Sp. z o.o., Tel.: +48 22 335 61 00
- **Portugal:** Laboratórios Pfizer, Lda., Tel: +351 21 423 5500
- **România:** Pfizer Romania S.R.L, Tel: +40 (0) 21 207 28 00
- **Slovenija:** Pfizer Luxembourg SARL, Pfizer, podružnica za svetovanje s področja farmacevtske dejavnosti, Ljubljana, Tel.: +386 (0) 1 52 11 400
- **Slovenská republika:** Pfizer Luxembourg SARL, organizačná zložka, Tel: +421 2 3355 5500
- **Suomi/Finland:** Pfizer Oy, Puh/Tel: +358 (0)9 430 040
- **Sverige:** Pfizer AB, Tel: +46 (0)8 550 520 00
- **United Kingdom (Northern Ireland):** Pfizer Limited, Tel: +44 (0) 1304 616161

This leaflet was last revised in

Scan the code with a mobile device to get the package leaflet in different languages.



URL: www.comirnatyglobal.com

Detailed information on this medicine is available on the European Medicines Agency website: <http://www.ema.europa.eu>.

The following information is intended for healthcare professionals only:

The dose of Comirnaty Original/Omicron BA.1 is 0.3 mL given intramuscularly.

Comirnaty Original/Omicron BA.1 is only indicated for individuals who have previously received at least a primary vaccination course against COVID-19.

There should be an interval of at least 3 months between administration of Comirnaty Original/Omicron BA.1 and the last prior dose of a COVID-19 vaccine.

Additional doses may be given to individuals who are severely immunocompromised.

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.

Handling instructions prior to use

Comirnaty Original/Omicron BA.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 **grey plastic cap** and the product **name is Comirnaty Original/Omicron BA.1 (15/15 micrograms)/dose dispersion for injection** (12 years and older).
- If the vial has another product name on the label, please make reference to the Summary of Product Characteristics 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 6 hours to thaw. Ensure vials are completely thawed prior to use.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Preparation of 0.3 mL doses

- Gently mix by inverting vials 10 times prior to use. Do not shake.
- Prior to mixing, the thawed dispersion may contain white to off-white opaque amorphous particles.
- After mixing, the vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the vaccine if particulates or discolouration are present.
- Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
- Withdraw 0.3 mL of Comirnaty Original/Omicron BA.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 vial. Discard any unused vaccine 12 hours after first puncture.

Disposal

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

Package leaflet: Information for the user

Comirnaty Original/Omicron BA.4-5 (15/15 micrograms)/dose dispersion for injection Adults and adolescents from 12 years COVID-19 mRNA Vaccine tozinameran/famtozinameran

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you receive this vaccine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Comirnaty Original/Omicron BA.4-5 is and what it is used for
2. What you need to know before you receive Comirnaty Original/Omicron BA.4-5
3. How Comirnaty Original/Omicron BA.4-5 is given
4. Possible side effects
5. How to store Comirnaty Original/Omicron BA.4-5
6. Contents of the pack and other information

1. What Comirnaty Original/Omicron BA.4-5 is and what it is used for

Comirnaty Original/Omicron BA.4-5 is a vaccine used for preventing COVID-19 caused by SARS-CoV-2. It is given to adults and adolescents from 12 years of age and older.

The vaccine causes the immune system (the body's natural defences) to produce antibodies and blood cells that work against the virus, so giving protection against COVID-19.

As Comirnaty Original/Omicron BA.4-5 does not contain the virus to produce immunity, it cannot give you COVID-19.

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

2. What you need to know before you receive Comirnaty Original/Omicron BA.4-5

Comirnaty Original/Omicron BA.4-5 should not be given

- if you are allergic to the active substance or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions

Talk to your doctor, pharmacist or nurse before you are given the vaccine if:

- you have ever had a severe allergic reaction or breathing problems after any other vaccine injection or after you were given this vaccine in the past.
- you are feeling nervous about the vaccination process or have ever fainted following any needle injection.
- you have a severe illness or infection with high fever. However, you can have your vaccination if you have a mild fever or upper airway infection like a cold.

- you have a bleeding problem, you bruise easily or you use a medicine to prevent blood-clots.
- you have a weakened immune system, because of a disease such as HIV infection or a medicine such as corticosteroid that affects your immune system.

There is an increased risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) after vaccination with Comirnaty (see section 4). 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. The risk of myocarditis and pericarditis seems lower in children ages 5 to 11 years compared with ages 12 to 17 years. Most cases of myocarditis and pericarditis recover. Some cases required intensive care support and fatal cases have been seen. Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

As with any vaccine, Comirnaty Original/Omicron BA.4-5 may not fully protect all those who receive it and it is not known how long you will be protected.

The efficacy of Comirnaty Original/Omicron BA.4-5 may be lower in people who are immunocompromised. If you are immunocompromised, you may receive additional doses of Comirnaty Original/Omicron BA.4-5. In these cases, you should continue to maintain physical precautions to help prevent COVID-19. In addition, your close contacts should be vaccinated as appropriate. Discuss appropriate individual recommendations with your doctor.

Children

Comirnaty Original/Omicron BA.4-5 (15/15 micrograms)/dose dispersion for injection is not recommended for children aged under 12 years.

There are paediatric formulations available for infants aged 6 months and above and children below 12 years of age. For details, please refer to the Package Leaflet for other formulations.

The vaccine is not recommended for infants aged under 6 months.

Other medicines and Comirnaty Original/Omicron BA.4-5

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines or have recently received any other vaccine.

Pregnancy and breast-feeding

If you are pregnant or think you may be pregnant, tell your doctor, nurse or pharmacist before you receive this vaccine.

No data are available yet regarding the use of Comirnaty Original/Omicron BA.4-5 during pregnancy. However, a large amount of information from pregnant women vaccinated with the initially approved Comirnaty vaccine during the second and third trimester have not shown negative effects on the pregnancy or the newborn baby. While information on effects on pregnancy or the newborn baby after vaccination during the first trimester is limited, no change to the risk for miscarriage has been seen. Comirnaty Original/Omicron BA.4-5 can be used during pregnancy.

No data are available yet regarding the use of Comirnaty Original/Omicron BA.4-5 during breast-feeding. However, no effects on the breastfed newborn/infant are anticipated. 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 Original/Omicron BA.4-5 can be used while breast-feeding.

Driving and using machines

Some of the effects of vaccination mentioned in section 4 (Possible side effects) may temporarily affect your ability to drive or use machines. Wait until these effects have worn off before you drive or use machines.

3. How Comirnaty Original/Omicron BA.4-5 is given

Comirnaty Original/Omicron BA.4-5 is given as an injection of 0.3 mL into a muscle of your upper arm.

You will receive 1 injection, regardless whether you have received a COVID-19 vaccine before.

If you were previously vaccinated with a COVID-19 vaccine, you should not receive a dose of Comirnaty Original/Omicron BA.4-5 until at least 3 months after the most recent dose.

If you are immunocompromised, you may receive additional doses of Comirnaty Original/Omicron BA.4-5.

If you have any further questions on the use of Comirnaty Original/Omicron BA.4-5, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all vaccines, Comirnaty Original/Omicron BA.4-5 can cause side effects, although not everybody gets them.

Very common side effects: may affect more than 1 in 10 people

- injection site: pain, swelling
- tiredness, headache
- muscle pain, joint pain
- chills, fever
- diarrhoea

Some of these side effects were slightly more frequent in adolescents 12 to 15 years than in adults.

Common side effects: may affect up to 1 in 10 people

- injection site redness
- nausea, vomiting
- enlarged lymph nodes (more frequently observed after a booster dose)

Uncommon side effects: may affect up to 1 in 100 people

- feeling unwell, feeling weak or lack of energy/sleepy
- arm pain
- insomnia
- injection site itching
- allergic reactions such as rash or itching
- decreased appetite
- dizziness
- excessive sweating, night sweats

Rare side effects: may affect up to 1 in 1 000 people

- temporary one sided facial drooping
- allergic reactions such as hives or swelling of the face

Very rare side effects: may affect up to 1 in 10 000 people

- inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain

Not known (cannot be estimated from the available data)

- severe allergic reaction
- extensive swelling of the vaccinated limb
- swelling of the face (swelling of the face may occur in patients who have had facial dermatological fillers)
- a skin reaction that causes red spots or patches on the skin, that may look like a target or “bulls-eye” with a dark red centre surrounded by paler red rings (erythema multiforme)
- unusual feeling in the skin, such as tingling or a crawling feeling (paraesthesia)
- decreased feeling or sensitivity, especially in the skin (hypoesthesia)
- heavy menstrual bleeding (most cases appeared to be non-serious and temporary in nature)

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system](#) listed in [Appendix V](#) and include batch/Lot number if available. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Comirnaty Original/Omicron BA.4-5

Keep this medicine out of the sight and reach of children.

The following information about storage, expiry and use and handling is intended for healthcare professionals.

Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.

Store in freezer at -90 °C to -60 °C.

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

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.

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 or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Multidose vials: 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 6 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed vials: Once removed from the freezer, the unopened vial may be stored and transported refrigerated at 2 °C to 8 °C for up to 10 weeks; not exceeding the printed expiry date (EXP). The outer carton should be marked with the new discard date at 2 °C to 8 °C. Once thawed, the vaccine cannot be re-frozen.

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

Thawed vials can be handled in room light conditions.

Opened vials: After first puncture, store the vaccine at 2 °C to 30 °C and use within 12 hours, which includes up to 6 hours transportation time. Discard any unused vaccine.

Do not use this vaccine if you notice particulates or discoloration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Comirnaty Original/Omicron BA.4-5 contains

- The active substances of COVID-19 mRNA Vaccine (nucleoside modified) are called tozinameran and famtozinameran.
 - A single dose vial contains 1 dose of 0.3 mL with 15 micrograms of tozinameran (Original) and 15 micrograms of famtozinameran (Omicron BA.4-5) per dose.
 - A multidose vial contains 6 doses of 0.3 mL with 15 micrograms of tozinameran (Original) and 15 micrograms of famtozinameran (Omicron BA.4-5) per dose.
- The other ingredients are:
 - ((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

What Comirnaty Original/Omicron BA.4-5 looks like and contents of the pack

The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9) provided in either:

- A single dose vial of 1 dose in a 2 mL clear vial (type I glass), with a rubber stopper and a grey flip-off plastic cap with aluminium seal; or
- A multidose vial of 6 doses in a 2 mL clear vial (type I glass), with a rubber stopper and a grey flip-off plastic cap with aluminium seal.

Single dose vial pack size: 10 vials

Multidose vial pack sizes: 10 vials or 195 vials

Not all pack sizes may be marketed.

Marketing Authorisation Holder

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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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- **Slovenija:** Pfizer Luxembourg SARL, Pfizer, podružnica za svetovanje s področja farmacevtske dejavnosti, Ljubljana, Tel.: +386 (0) 1 52 11 400
- **Slovenská republika:** Pfizer Luxembourg SARL, organizačná zložka, Tel: +421 2 3355 5500
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- **United Kingdom (Northern Ireland):** Pfizer Limited, Tel: +44 (0) 1304 616161

This leaflet was last revised in

Scan the code with a mobile device to get the package leaflet in different languages.



URL: www.comirnatyglobal.com

Detailed information on this medicine is available on the European Medicines Agency website:
<http://www.ema.europa.eu>

The following information is intended for healthcare professionals only:

Administer Comirnaty Original/Omicron BA.4-5 intramuscularly as a single dose of 0.3 mL regardless of prior COVID-19 vaccination status.

For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty Original/Omicron BA.4-5 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Additional doses may be given to individuals who are severely immunocompromised.

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.

Handling instructions prior to use

Comirnaty Original/Omicron BA.4-5 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- **Verify** that the vial has a **grey plastic cap** and the product **name is Comirnaty Original/Omicron BA.4-5 (15/15 micrograms)/dose dispersion for injection** (12 years and older).
- If the vial has another product name on the label, please make reference to the Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw. Ensure vials are completely thawed prior to use.
 - 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).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Preparation of 0.3 mL doses

- Gently mix by inverting vials 10 times prior to use. Do not shake.
- Prior to mixing, the thawed dispersion may contain white to off-white opaque amorphous particles.
- After mixing, the vaccine should present as a white to off-white 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 Original/Omicron BA.4-5.

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 vial. Discard any unused vaccine 12 hours after first puncture.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Package leaflet: Information for the user

Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose concentrate for dispersion for injection

Children 5 to 11 years
COVID-19 mRNA Vaccine
tozinameran/famtozinameran

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects your child may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before your child receives this vaccine because it contains important information for your child.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your child's doctor, pharmacist or nurse.
- If your child gets any side effects, talk to your child's doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Comirnaty Original/Omicron BA.4-5 is and what it is used for
2. What you need to know before your child receives Comirnaty Original/Omicron BA.4-5
3. How Comirnaty Original/Omicron BA.4-5 is given
4. Possible side effects
5. How to store Comirnaty Original/Omicron BA.4-5
6. Contents of the pack and other information

1. What Comirnaty Original/Omicron BA.4-5 is and what it is used for

Comirnaty Original/Omicron BA.4-5 is a vaccine used for preventing COVID-19 caused by SARS-CoV-2. It is given to children from 5 to 11 years of age.

The vaccine causes the immune system (the body's natural defences) to produce antibodies and blood cells that work against the virus, so giving protection against COVID-19.

As Comirnaty Original/Omicron BA.4-5 does not contain the virus to produce immunity, it cannot give your child COVID-19.

The use of this vaccine should be in accordance with official recommendations.

2. What you need to know before your child receives Comirnaty Original/Omicron BA.4-5

Comirnaty Original/Omicron BA.4-5 should not be given

- if your child is allergic to the active substance or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions

Talk to your child's doctor, pharmacist or nurse before your child is given the vaccine if your child:

- has ever had a severe allergic reaction or breathing problems after any other vaccine injection or after having been given this vaccine in the past.
- is feeling nervous about the vaccination process or has ever fainted following any needle injection.
- has a severe illness or infection with high fever. However, your child can have the vaccination if he/she has a mild fever or upper airway infection like a cold.

- has a bleeding problem, bruises easily or uses a medicine to prevent blood-clots.
- has a weakened immune system, because of a disease such as HIV infection or a medicine such as corticosteroid that affects the immune system.

There is an increased risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) after vaccination with Comirnaty (see section 4). 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. The risk of myocarditis and pericarditis seems lower in children ages 5 to 11 years compared with ages 12 to 17 years. Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

As with any vaccine, Comirnaty Original/Omicron BA.4-5 may not fully protect all those who receive it and it is not known how long your child will be protected.

The efficacy of Comirnaty Original/Omicron BA.4-5 may be lower in people who are immunocompromised. If your child is immunocompromised, he/she may receive additional doses of Comirnaty Original/Omicron BA.4-5. In these cases, your child should continue to maintain physical precautions to help prevent COVID-19. In addition, your child's close contacts should be vaccinated as appropriate. Discuss appropriate individual recommendations with your child's doctor.

Children

Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose concentrate for dispersion for injection is not recommended for children aged under 5 years.

There are paediatric formulations available for infants and children aged 6 months to 4 years. For details, please refer to the Package Leaflet for other formulations.

The vaccine is not recommended for infants aged under 6 months.

Other medicines and Comirnaty Original/Omicron BA.4-5

Tell your child's doctor or pharmacist if your child is using, has recently used or might use any other medicines or has recently received any other vaccine.

Pregnancy and breast-feeding

If your child is pregnant, tell your child's doctor, nurse or pharmacist before your child receives this vaccine.

No data are available yet regarding the use of Comirnaty Original/Omicron BA.4-5 during pregnancy. However, a large amount of information from pregnant women vaccinated with the initially approved Comirnaty vaccine during the second and third trimester have not shown negative effects on the pregnancy or the newborn baby. While information on effects on pregnancy or the newborn baby after vaccination during the first trimester is limited, no change to the risk for miscarriage has been seen. Comirnaty Original/Omicron BA.4-5 can be used during pregnancy.

No data are available yet regarding the use of Comirnaty Original/Omicron BA.4-5 during breast-feeding. However, no effects on the breastfed newborn/infant are anticipated. 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 Original/Omicron BA.4-5 can be used while breast-feeding.

Driving and using machines

Some of the effects of vaccination mentioned in section 4 (Possible side effects) may temporarily affect your child's ability to use machines or undertake activities such as cycling. Wait until these effects have worn off before resuming activities that require your child's full attention.

3. How Comirnaty Original/Omicron BA.4-5 is given

Comirnaty Original/Omicron BA.4-5 is given after dilution as an injection of 0.2 mL into a muscle of your child's upper arm.

Your child will receive 1 injection, regardless whether he/she has received a COVID-19 vaccine before.

If your child was previously vaccinated with a COVID-19 vaccine, he/she should not receive a dose of Comirnaty Original/Omicron BA.4-5 until at least 3 months after the most recent dose.

If your child is immunocompromised, he/she may receive additional doses of Comirnaty Original/Omicron BA.4-5.

If you have any further questions on the use of Comirnaty Original/Omicron BA.4-5, ask your child's doctor, pharmacist or nurse.

4. Possible side effects

Like all vaccines, Comirnaty Original/Omicron BA.4-5 can cause side effects, although not everybody gets them.

Very common side effects: may affect more than 1 in 10 people

- injection site: pain, swelling
- tiredness, headache
- muscle pain, joint pain
- chills, fever
- diarrhoea

Common side effects: may affect up to 1 in 10 people

- nausea, vomiting
- injection site redness ('very common' in 5 to 11 years of age)
- enlarged lymph nodes (more frequently observed after a booster dose)

Uncommon side effects: may affect up to 1 in 100 people

- feeling unwell, feeling weak or lack of energy/sleepy
- arm pain
- insomnia
- injection site itching
- allergic reactions such as rash or itching
- decreased appetite
- dizziness
- excessive sweating, night sweats

Rare side effects: may affect up to 1 in 1 000 people

- temporary one sided facial drooping
- allergic reactions such as hives or swelling of the face

Very rare side effects: may affect up to 1 in 10 000 people

- inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain

Not known (cannot be estimated from the available data)

- severe allergic reaction
- extensive swelling of the vaccinated limb
- swelling of the face (swelling of the face may occur in patients who have had facial dermatological fillers)
- a skin reaction that causes red spots or patches on the skin, that may look like a target or “bulls-eye” with a dark red centre surrounded by paler red rings (erythema multiforme)
- unusual feeling in the skin, such as tingling or a crawling feeling (paraesthesia)
- decreased feeling or sensitivity, especially in the skin (hypoesthesia)
- heavy menstrual bleeding (most cases appeared to be non-serious and temporary in nature)

Reporting of side effects

If your child gets any side effects, talk to your child’s doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system](#) listed in [Appendix V](#) and include batch/Lot number if available. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Comirnaty Original/Omicron BA.4-5

Keep this medicine out of the sight and reach of children.

The following information about storage, expiry and use and handling is intended for healthcare professionals.

Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.

Store in freezer at -90 °C to -60 °C.

Store in the original package in order to protect from light.

The vaccine will be received frozen at -90 °C to -60 °C. Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

When stored frozen at -90 °C to -60 °C, 10-vial packs of the vaccine can be thawed at 2 °C to 8 °C for 4 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Once removed from the freezer, the unopened vial may be stored and transported refrigerated at 2 °C to 8 °C for up to 10 weeks; not exceeding the printed expiry date (EXP). The outer carton should be marked with the new discard date at 2 °C to 8 °C. Once thawed, the vaccine cannot be re-frozen.

Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between 8 °C and 30 °C.

Thawed vials can be handled in room light conditions.

After dilution, store the vaccine at 2 °C to 30 °C and use within 12 hours, which includes up to 6 hours transportation time. Discard any unused vaccine.

Do not use this vaccine if you notice particulates in the dilution or discolouration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Comirnaty Original/Omicron BA.4-5 contains

- The active substances of COVID-19 mRNA Vaccine (nucleoside modified) are called tozinameran and famtozinameran. After dilution, the vial contains 10 doses of 0.2 mL with 5 micrograms of tozinameran (Original) and 5 micrograms of famtozinameran (Omicron BA.4-5) per dose.
- The other ingredients are:
 - ((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

What Comirnaty Original/Omicron BA.4-5 looks like and contents of the pack

The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9) provided in a multidose vial of 10 doses in a 2 mL clear vial (type I glass), with a rubber stopper and an orange flip-off plastic cap with aluminium seal.

Pack sizes: 10 vials or 195 vials

Not all pack sizes may be marketed.

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- **Sverige:** Pfizer AB, Tel: +46 (0)8 550 520 00
- **United Kingdom (Northern Ireland):** Pfizer Limited, Tel: +44 (0) 1304 616161

This leaflet was last revised in

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URL: www.comirnatyglobal.com

Detailed information on this medicine is available on the European Medicines Agency website:
<http://www.ema.europa.eu>

The following information is intended for healthcare professionals only:

Administer Comirnaty Original/Omicron BA.4-5 intramuscularly after dilution as a single dose of 0.2 mL regardless of prior COVID-19 vaccination status.

For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty Original/Omicron BA.4-5 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Additional doses may be given to individuals who are severely immunocompromised.

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.

Handling instructions prior to use

Comirnaty Original/Omicron BA.4-5 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- **Verify** that the vial has an **orange plastic cap** and the product **name is Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose concentrate for dispersion for injection** (children 5 to 11 years).
- If the vial has another product name on the label, please make reference to the Summary of Product Characteristics 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 4 hours to thaw. Ensure vials are completely thawed prior to use.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Dilution

- 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 **1.3 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 1.3 mL air into the empty diluent syringe.
- Gently invert the diluted dispersion 10 times. Do not shake.
- The diluted vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discolouration are present.
- The diluted vials should be marked with the appropriate **discard date and time**.
- **After dilution**, store at 2 °C to 30 °C and use within **12 hours**.
- Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.

Preparation of 0.2 mL doses

- 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 Original/Omicron BA.4-5 for children aged 5 to 11 years. **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 12 hours after dilution.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Package leaflet: Information for the user

Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose dispersion for injection Children 5 to 11 years COVID-19 mRNA Vaccine tozinameran/famtozinameran

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects your child may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before your child receives this vaccine because it contains important information for your child.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your child's doctor, pharmacist or nurse.
- If your child gets any side effects, talk to your child's doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Comirnaty Original/Omicron BA.4-5 is and what it is used for
2. What you need to know before your child receives Comirnaty Original/Omicron BA.4-5
3. How Comirnaty Original/Omicron BA.4-5 is given
4. Possible side effects
5. How to store Comirnaty Original/Omicron BA.4-5
6. Contents of the pack and other information

1. What Comirnaty Original/Omicron BA.4-5 is and what it is used for

Comirnaty Original/Omicron BA.4-5 is a vaccine used for preventing COVID-19 caused by SARS-CoV-2. It is given to children from 5 to 11 years of age.

The vaccine causes the immune system (the body's natural defences) to produce antibodies and blood cells that work against the virus, so giving protection against COVID-19.

As Comirnaty Original/Omicron BA.4-5 does not contain the virus to produce immunity, it cannot give your child COVID-19.

The use of this vaccine should be in accordance with official recommendations.

2. What you need to know before your child receives Comirnaty Original/Omicron BA.4-5

Comirnaty Original/Omicron BA.4-5 should not be given

- if your child is allergic to the active substance or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions

Talk to your child's doctor, pharmacist or nurse before your child is given the vaccine if your child:

- has ever had a severe allergic reaction or breathing problems after any other vaccine injection or after having been given this vaccine in the past.
- is feeling nervous about the vaccination process or has ever fainted following any needle injection.
- has a severe illness or infection with high fever. However, your child can have the vaccination if he/she has a mild fever or upper airway infection like a cold.

- has a bleeding problem, bruises easily or uses a medicine to prevent blood-clots.
- has a weakened immune system, because of a disease such as HIV infection or a medicine such as corticosteroid that affects the immune system.

There is an increased risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) after vaccination with Comirnaty (see section 4). 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. The risk of myocarditis and pericarditis seems lower in children ages 5 to 11 years compared with ages 12 to 17 years. Most cases of myocarditis and pericarditis recover. Some cases required intensive care support and fatal cases have been seen. Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

As with any vaccine, Comirnaty Original/Omicron BA.4-5 may not fully protect all those who receive it and it is not known how long your child will be protected.

The efficacy of Comirnaty Original/Omicron BA.4-5 may be lower in people who are immunocompromised. If your child is immunocompromised, he/she may receive additional doses of Comirnaty Original/Omicron BA.4-5. In these cases, your child should continue to maintain physical precautions to help prevent COVID-19. In addition, your child's close contacts should be vaccinated as appropriate. Discuss appropriate individual recommendations with your child's doctor.

Children

Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose dispersion for injection is not recommended for children aged under 5 years.

There are paediatric formulations available for infants and children aged 6 months to 4 years. For details, please refer to the Package Leaflet for other formulations.

The vaccine is not recommended for infants aged under 6 months.

Other medicines and Comirnaty Original/Omicron BA.4-5

Tell your child's doctor or pharmacist if your child is using, has recently used or might use any other medicines or has recently received any other vaccine.

Pregnancy and breast-feeding

If your child is pregnant, tell your child's doctor, nurse or pharmacist before your child receives this vaccine.

No data are available yet regarding the use of Comirnaty Original/Omicron BA.4-5 during pregnancy. However, a large amount of information from pregnant women vaccinated with the initially approved Comirnaty vaccine during the second and third trimester have not shown negative effects on the pregnancy or the newborn baby. While information on effects on pregnancy or the newborn baby after vaccination during the first trimester is limited, no change to the risk for miscarriage has been seen. Comirnaty Original/Omicron BA.4-5 can be used during pregnancy.

No data are available yet regarding the use of Comirnaty Original/Omicron BA.4-5 during breast-feeding. However, no effects on the breastfed newborn/infant are anticipated. 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 Original/Omicron BA.4-5 can be used while breast-feeding.

Driving and using machines

Some of the effects of vaccination mentioned in section 4 (Possible side effects) may temporarily affect your child's ability to use machines or undertake activities such as cycling. Wait until these effects have worn off before resuming activities that require your child's full attention.

3. How Comirnaty Original/Omicron BA.4-5 is given

Comirnaty Original/Omicron BA.4-5 is given as an injection of 0.3 mL into a muscle of your child's upper arm.

Your child will receive 1 injection, regardless whether he/she has received a COVID-19 vaccine before.

If your child was previously vaccinated with a COVID-19 vaccine, he/she should not receive a dose of Comirnaty Original/Omicron BA.4-5 until at least 3 months after the most recent dose.

If your child is immunocompromised, your child may receive additional doses of Comirnaty Original/Omicron BA.4-5.

If you have any further questions on the use of Comirnaty Original/Omicron BA.4-5, ask your child's doctor, pharmacist or nurse.

4. Possible side effects

Like all vaccines, Comirnaty Original/Omicron BA.4-5 can cause side effects, although not everybody gets them.

Very common side effects: may affect more than 1 in 10 people

- injection site: pain, swelling
- tiredness, headache
- muscle pain, joint pain
- chills, fever
- diarrhoea

Common side effects: may affect up to 1 in 10 people

- nausea, vomiting
- injection site redness ('very common' in 5 to 11 years of age)
- enlarged lymph nodes (more frequently observed after a booster dose)

Uncommon side effects: may affect up to 1 in 100 people

- feeling unwell, feeling weak or lack of energy/sleepy
- arm pain
- insomnia
- injection site itching
- allergic reactions such as rash or itching
- decreased appetite
- dizziness
- excessive sweating, night sweats

Rare side effects: may affect up to 1 in 1 000 people

- temporary one sided facial drooping
- allergic reactions such as hives or swelling of the face

Very rare side effects: may affect up to 1 in 10 000 people

- inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain

Not known (cannot be estimated from the available data)

- severe allergic reaction
- extensive swelling of the vaccinated limb
- swelling of the face (swelling of the face may occur in patients who have had facial dermatological fillers)
- a skin reaction that causes red spots or patches on the skin, that may look like a target or “bulls-eye” with a dark red centre surrounded by paler red rings (erythema multiforme)
- unusual feeling in the skin, such as tingling or a crawling feeling (paraesthesia)
- decreased feeling or sensitivity, especially in the skin (hypoesthesia)
- heavy menstrual bleeding (most cases appeared to be non-serious and temporary in nature)

Reporting of side effects

If your child gets any side effects, talk to your child’s doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system](#) listed in [Appendix V](#) and include batch/Lot number if available. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Comirnaty Original/Omicron BA.4-5

Keep this medicine out of the sight and reach of children.

The following information about storage, expiry and use and handling is intended for healthcare professionals.

Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.

Store in freezer at -90 °C to -60 °C.

Store in the original package in order to protect from light.

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.

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 or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Multidose vials: 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 6 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed vials: Once removed from the freezer, the unopened vial may be stored and transported refrigerated at 2 °C to 8 °C for up to 10 weeks; not exceeding the printed expiry date (EXP). The outer carton should be marked with the new discard date at 2 °C to 8 °C. Once thawed, the vaccine cannot be re-frozen.

Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between 8 °C and 30 °C.

Thawed vials can be handled in room light conditions.

Opened vials: After first puncture, store the vaccine at 2 °C to 30 °C and use within 12 hours, which includes up to 6 hours transportation time. Discard any unused vaccine.

Do not use this vaccine if you notice particulates or discolouration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Comirnaty Original/Omicron BA.4-5 contains

- The active substances of COVID-19 mRNA Vaccine (nucleoside modified) are called tozinameran and famtozinameran.
 - A single dose vial contains 1 dose of 0.3 mL with 5 micrograms of tozinameran (Original) and 5 micrograms of famtozinameran (Omicron BA.4-5) per dose.
 - A multidose vial contains 6 doses of 0.3 mL with 5 micrograms of tozinameran (Original) and 5 micrograms of famtozinameran (Omicron BA.4-5) per dose.
- The other ingredients are:
 - ((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

What Comirnaty Original/Omicron BA.4-5 looks like and contents of the pack

The vaccine is a clear to slightly opalescent dispersion (pH: 6.9 - 7.9) provided in either:

- A single dose vial of 1 dose in a 2 mL clear vial (type I glass), with a rubber stopper and a blue flip-off plastic cap with aluminium seal; or
- A multidose vial of 6 doses in a 2 mL clear vial (type I glass), with a rubber stopper and a blue flip-off plastic cap with aluminium seal.

Single dose vial pack size: 10 vials

Multidose vial pack size: 10 vials

Not all pack sizes may be marketed.

Marketing Authorisation Holder

BioNTech Manufacturing GmbH

An der Goldgrube 12

55131 Mainz

Germany

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Manufacturers

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Kupferbergterrasse 17 - 19

55116 Mainz

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Pfizer Manufacturing Belgium NV

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Puurs-Sint-Amands, 2870

Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

- **België/Belgique/Belgien, Luxembourg/Luxemburg:** Pfizer S.A./N.V.,
Tél/Tel: +32 (0)2 554 62 11
- **България:** Пфайзер Люксембург САРЛ, Клон, България, Тел: +359 2 970 4333
- **Česká republika:** Pfizer, spol. s r.o., Tel: +420 283 004 111
- **Danmark:** Pfizer ApS, Tlf: +45 44 201 100
- **Deutschland:** BioNTech Manufacturing GmbH, Tel: +49 6131 90840
- **Eesti:** Pfizer Luxembourg SARL Eesti filiaal, Tel: +372 666 7500
- **Ελλάδα:** Pfizer Ελλάς Α.Ε., Τηλ.: +30 210 6785 800
- **España:** Pfizer, S.L., Tel: +34914909900
- **France:** Pfizer, Tél +33 1 58 07 34 40
- **Hrvatska:** Pfizer Croatia d.o.o., Tel: +385 1 3908 777
- **Ireland:** Pfizer Healthcare Ireland, Tel: 1800 633 363 (toll free), +44 (0)1304 616161
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- **Κύπρος:** Pfizer Ελλάς Α.Ε. (Cyprus Branch), Τηλ: +357 22 817690
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- **Lietuva:** Pfizer Luxembourg SARL filialas Lietuvoje, Tel. +370 52 51 4000
- **Magyarország:** Pfizer Kft, Tel: +36 1 488 3700
- **Malta:** Vivian Corporation Ltd., Tel: +35621 344610
- **Norge:** Pfizer AS, Tlf: +47 67 526 100
- **Nederland:** Pfizer BV, Tel: +31 (0)10 406 43 01
- **Österreich:** Pfizer Corporation Austria Ges.m.b.H, Tel: +43 (0)1 521 15-0
- **Polska:** Pfizer Polska Sp. z o.o., Tel.: +48 22 335 61 00
- **Portugal:** Laboratórios Pfizer, Lda., Tel: +351 21 423 5500
- **România:** Pfizer Romania S.R.L, Tel: +40 (0) 21 207 28 00
- **Slovenija:** Pfizer Luxembourg SARL, Pfizer, podružnica za svetovanje s področja farmacevtske dejavnosti, Ljubljana, Tel.: +386 (0) 1 52 11 400
- **Slovenská republika:** Pfizer Luxembourg SARL, organizačná zložka, Tel: +421 2 3355 5500
- **Suomi/Finland:** Pfizer Oy, Puh/Tel: +358 (0)9 430 040
- **Sverige:** Pfizer AB, Tel: +46 (0)8 550 520 00
- **United Kingdom (Northern Ireland):** Pfizer Limited, Tel: +44 (0) 1304 616161

This leaflet was last revised in

Scan the code with a mobile device to get the package leaflet in different languages.



URL: www.comirnatyglobal.com

Detailed information on this medicine is available on the European Medicines Agency website:
<http://www.ema.europa.eu>

The following information is intended for healthcare professionals only:

Administer Comirnaty Original/Omicron BA.4-5 intramuscularly as a single dose of 0.3 mL regardless of prior COVID-19 vaccination status.

For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty Original/Omicron BA.4-5 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Additional doses may be given to individuals who are severely immunocompromised.

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.

Handling instructions prior to use

Comirnaty Original/Omicron BA.4-5 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- **Verify** that the vial has a **blue plastic cap** and the product **name is Comirnaty Original/Omicron BA.4-5 (5/5 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 Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw. Ensure vials are completely thawed prior to use.
 - 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).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Preparation of 0.3 mL doses

- Gently mix by inverting vials 10 times prior to use. Do not shake.
- Prior to mixing, the thawed dispersion may contain white to off-white opaque amorphous particles.
- After mixing, the vaccine should present as a clear to slightly opalescent dispersion with no particulates visible. Do not use the vaccine if particulates or discoloration 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 Original/Omicron BA.4-5 for children aged 5 to 11 years.

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 vial. Discard any unused vaccine 12 hours after first puncture.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Package leaflet: Information for the user

Comirnaty Original/Omicron BA.4-5 (1.5/1.5 micrograms)/dose concentrate for dispersion for injection

Infants and children 6 months to 4 years

COVID-19 mRNA Vaccine

tozinameran/famtozinameran

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects your child may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before your child receives this vaccine because it contains important information for your child.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your child's doctor, pharmacist or nurse.
- If your child gets any side effects, talk to your child's doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Comirnaty Original/Omicron BA.4-5 is and what it is used for
2. What you need to know before your child receives Comirnaty Original/Omicron BA.4-5
3. How Comirnaty Original/Omicron BA.4-5 is given
4. Possible side effects
5. How to store Comirnaty Original/Omicron BA.4-5
6. Contents of the pack and other information

1. What Comirnaty Original/Omicron BA.4-5 is and what it is used for

Comirnaty Original/Omicron BA.4-5 is a vaccine used for preventing COVID-19 caused by SARS-CoV-2. It is given to infants and children from 6 months to 4 years of age.

The vaccine causes the immune system (the body's natural defences) to produce antibodies and blood cells that work against the virus, so giving protection against COVID-19.

As Comirnaty Original/Omicron BA.4-5 does not contain the virus to produce immunity, it cannot give your child COVID-19.

The use of this vaccine should be in accordance with official recommendations.

2. What you need to know before your child receives Comirnaty Original/Omicron BA.4-5

Comirnaty Original/Omicron BA.4-5 should not be given

- if your child is allergic to the active substance or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions

Talk to your child's doctor, pharmacist or nurse before your child is given the vaccine if your child:

- has ever had a severe allergic reaction or breathing problems after any other vaccine injection or after having been given this vaccine in the past.
- is feeling nervous about the vaccination process or has ever fainted following any needle injection.
- has a severe illness or infection with high fever. However, your child can have the vaccination if he/she has a mild fever or upper airway infection like a cold.

- has a bleeding problem, bruises easily or uses a medicine to prevent blood-clots.
- has a weakened immune system, because of a disease such as HIV infection or a medicine such as corticosteroid that affects the immune system.

There is an increased risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) after vaccination with Comirnaty (see section 4). 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. The risk of myocarditis and pericarditis seems lower in children ages 5 to 11 years compared with ages 12 to 17 years. Most cases of myocarditis and pericarditis recover. Some cases required intensive care support and fatal cases have been seen. Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

As with any vaccine, Comirnaty Original/Omicron BA.4-5 may not fully protect all those who receive it and it is not known how long your child will be protected.

The efficacy of Comirnaty Original/Omicron BA.4-5, may be lower in people who are immunocompromised. If your child is immunocompromised, he/she may receive additional doses of Comirnaty Original/Omicron BA.4-5. In these cases, your child should continue to maintain physical precautions to help prevent COVID-19. In addition, your child's close contacts should be vaccinated as appropriate. Discuss appropriate individual recommendations with your child's doctor.

Children

Comirnaty Original/Omicron BA.4-5 (1.5/1.5 micrograms)/dose concentrate for dispersion for injection is not recommended for children aged 5 years to 11 years.

There are paediatric formulations available for children 5 to 11 years of age. For details, please refer to the Package Leaflet for other formulations.

The vaccine is not recommended for infants aged under 6 months.

Other medicines and Comirnaty Original/Omicron BA.4-5

Tell your child's doctor or pharmacist if your child is using, has recently used or might use any other medicines or has recently received any other vaccine.

Pregnancy and breast-feeding

Comirnaty Original/Omicron BA.4-5 (1.5/1.5 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 Package Leaflet for those formulations.

Driving and using machines

Some of the effects of vaccination mentioned in section 4 (Possible side effects) may temporarily affect your child's ability to use machines or undertake activities such as cycling. Wait until these effects have worn off before resuming activities that require your child's full attention.

3. How Comirnaty Original/Omicron BA.4-5 is given

If your infant is from 6 months to less than 12 months of age, he/she will be given Comirnaty Original/Omicron BA.4-5 after dilution as an injection of 0.2 mL into a muscle of the thigh. If your infant or child is 1 year of age or older, he/she will be given Comirnaty Original/Omicron BA.4-5 after dilution as an injection of 0.2 mL into a muscle of the thigh or into a muscle of the upper arm.

If your child has not completed a COVID-19 primary vaccination course or has not been infected by COVID-19 in the past, your child will receive a maximum of 3 injections (the total number of doses required as primary course). It is recommended to receive the second dose 3 weeks after the first dose followed by a third dose at least 8 weeks after the second dose to complete the primary course.

If your child has previously completed a COVID-19 primary vaccination course or has had COVID-19 your child will receive 1 injection. If your child was previously vaccinated with a COVID-19 vaccine, your child should not receive a dose of Comirnaty Original/Omicron BA.4-5 until at least 3 months after the most recent dose.

If your 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.

If your child is immunocompromised, he/she may receive additional doses of Comirnaty Original/Omicron BA.4-5.

Interchangeability

Your child may receive either Comirnaty or Comirnaty Original/Omicron BA.4-5 (or a combination of both) for the primary course. Your child should not receive more than the total number of doses needed as primary course. Your child should only be administered the primary course once.

If you have any further questions on the use of Comirnaty Original/Omicron BA.4-5, ask your child's doctor, pharmacist or nurse.

4. Possible side effects

Like all vaccines, Comirnaty Original/Omicron BA.4-5 can cause side effects, although not everybody gets them.

Very common side effects: may affect more than 1 in 10 people

- irritability (6 months to < 2 years)
- injection site: pain/tenderness, swelling
- tiredness, headache
- drowsiness (6 months to < 2 years)
- muscle pain, joint pain
- chills, fever
- diarrhoea

Common side effects: may affect up to 1 in 10 people

- nausea, vomiting
- injection site redness ('very common' in 6 months to 11 years)
- enlarged lymph nodes (more frequently observed after a booster dose)

Uncommon side effects: may affect up to 1 in 100 people

- feeling unwell, feeling weak or lack of energy/sleepy
- arm pain
- insomnia
- injection site itching
- allergic reactions such as rash ('common' for 6 months to < 2 years) or itching
- decreased appetite ('very common' for 6 months to < 2 years)
- dizziness
- excessive sweating, night sweats

Rare side effects: may affect up to 1 in 1 000 people

- temporary one sided facial drooping
- allergic reactions such as hives or swelling of the face

Very rare side effects: may affect up to 1 in 10 000 people

- inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain

Not known (cannot be estimated from the available data)

- severe allergic reaction
- extensive swelling of the vaccinated limb
- swelling of the face (swelling of the face may occur in patients who have had facial dermatological fillers)
- a skin reaction that causes red spots or patches on the skin, that may look like a target or “bulls-eye” with a dark red centre surrounded by paler red rings (erythema multiforme)
- unusual feeling in the skin, such as tingling or a crawling feeling (paraesthesia)
- decreased feeling or sensitivity, especially in the skin (hypoesthesia)
- heavy menstrual bleeding (most cases appeared to be non-serious and temporary in nature)

Reporting of side effects

If your child gets any side effects, talk to your child’s doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system](#) listed in [Appendix V](#) and include batch/Lot number if available. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Comirnaty Original/Omicron BA.4-5

Keep this medicine out of the sight and reach of children.

The following information about storage, expiry and use and handling is intended for healthcare professionals.

Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.

Store in freezer at -90 °C to -60 °C.

Store in the original package in order to protect from light.

The vaccine will be received frozen at -90 °C to -60 °C. Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

When stored frozen at -90 °C to -60 °C, 10-vial packs of the vaccine can be thawed at 2 °C to 8 °C for 2 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Once removed from the freezer, the unopened vial may be stored and transported refrigerated at 2 °C to 8 °C for up to 10 weeks; not exceeding the printed expiry date (EXP). The outer carton should be marked with the new discard date at 2 °C to 8 °C. Once thawed, the vaccine cannot be re-frozen.

Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between 8 °C and 30 °C.

Thawed vials can be handled in room light conditions.

After dilution, store the vaccine at 2 °C to 30 °C and use within 12 hours, which includes up to 6 hours transportation time. Discard any unused vaccine.

Do not use this vaccine if you notice particulates in the dilution or discolouration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Comirnaty Original/Omicron BA.4-5 contains

- The active substances of COVID-19 mRNA Vaccine (nucleoside modified) are called tozinameran and famtozinameran. After dilution, the vial contains 10 doses of 0.2 mL with 1.5 micrograms of tozinameran (Original) and 1.5 micrograms of famtozinameran (Omicron BA.4-5) per dose.
- The other ingredients are:
 - ((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

What Comirnaty Original/Omicron BA.4-5 looks like and contents of the pack

The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9) provided in a multidose vial of 10 doses in a 2 mL clear vial (type I glass), with a rubber stopper and a maroon flip-off plastic cap with aluminium seal.

Pack size: 10 vials

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Scan the code with a mobile device to get the package leaflet in different languages.



URL: www.comirnatyglobal.com

Detailed information on this medicine is available on the European Medicines Agency website:
<http://www.ema.europa.eu>

The following information is intended for healthcare professionals only:

If the child has not completed a COVID-19 primary vaccination course or does not have a history of prior SARS-CoV-2 infection, administer Comirnaty Original/Omicron BA.4-5 intramuscularly after dilution as a primary course of maximum 3 doses (the total number of doses required as primary

course) (0.2 mL each); the second dose administered 3 weeks after the first dose followed by a third dose at least 8 weeks after the second dose to complete the primary course.

If the child has completed a COVID-19 primary vaccination course or has a history of prior SARS-CoV-2 infection, administer Comirnaty Original/Omicron BA.4-5 intramuscularly after dilution a single dose of 0.2 mL. If the individual was previously vaccinated with a COVID-19 vaccine, the individual should receive a dose of Comirnaty Original/Omicron BA.4-5 at least 3 months after the most recent dose.

Additional doses may be given to individuals who are severely immunocompromised.

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.

Handling instructions prior to use

Comirnaty Original/Omicron BA.4-5 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- **Verify** that the vial has a **maroon plastic cap** and the product **name is Comirnaty Original/Omicron BA.4-5 (1.5/1.5 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, please make reference to the Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 10-vial pack may take 2 hours to thaw. Ensure vials are completely thawed prior to use.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Dilution

- 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 **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 2.2 mL air into the empty diluent syringe.
- Gently invert the diluted dispersion 10 times. Do not shake.
- The diluted vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discolouration are present.
- The diluted vials should be marked with the appropriate **discard date and time**.
- **After dilution**, store at 2 °C to 30 °C and use within **12 hours**.
- Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.

Preparation of 0.2 mL doses

- 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 Original/Omicron BA.4-5 for infants and children aged 6 months to 4 years.

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 12 hours after dilution.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Package leaflet: Information for the user

Comirnaty Omicron XBB.1.5 30 micrograms/dose dispersion for injection Adults and adolescents from 12 years COVID-19 mRNA Vaccine raxtozinameran

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you receive this vaccine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Comirnaty Omicron XBB.1.5 is and what it is used for
2. What you need to know before you receive Comirnaty Omicron XBB.1.5
3. How Comirnaty Omicron XBB.1.5 is given
4. Possible side effects
5. How to store Comirnaty Omicron XBB.1.5
6. Contents of the pack and other information

1. What Comirnaty Omicron XBB.1.5 is and what it is used for

Comirnaty Omicron XBB.1.5 is a vaccine used for preventing COVID-19 caused by SARS-CoV-2.

Comirnaty Omicron XBB.1.5 30 micrograms/dose dispersion for injection is given to adults and adolescents from 12 years of age and older.

The vaccine causes the immune system (the body's natural defences) to produce antibodies and blood cells that work against the virus, so giving protection against COVID-19.

As Comirnaty Omicron XBB.1.5 does not contain the virus to produce immunity, it cannot give you COVID-19.

The use of this vaccine should be in accordance with official recommendations.

2. What you need to know before you receive Comirnaty Omicron XBB.1.5

Comirnaty Omicron XBB.1.5 should not be given

- if you are allergic to the active substance or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions

Talk to your doctor, pharmacist or nurse before you are given the vaccine if:

- you have ever had a severe allergic reaction or breathing problems after any other vaccine injection or after you were given this vaccine in the past.
- you are feeling nervous about the vaccination process or have ever fainted following any needle injection.

- you have a severe illness or infection with high fever. However, you can have your vaccination if you have a mild fever or upper airway infection like a cold.
- you have a bleeding problem, you bruise easily or you use a medicine to prevent blood-clots.
- you have a weakened immune system, because of a disease such as HIV infection or a medicine such as corticosteroid that affects your immune system.

There is an increased risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) after vaccination with Comirnaty (see section 4). 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. The risk of myocarditis and pericarditis seems lower in children ages 5 to 11 years compared with ages 12 to 17 years. Most cases of myocarditis and pericarditis recover. Some cases required intensive care support and fatal cases have been seen. Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

As with any vaccine, Comirnaty Omicron XBB.1.5 may not fully protect all those who receive it and it is not known how long you will be protected.

The efficacy of Comirnaty Omicron XBB.1.5 may be lower in people who are immunocompromised. If you are immunocompromised, you may receive additional doses of Comirnaty Omicron XBB.1.5. In these cases, you should continue to maintain physical precautions to help prevent COVID-19. In addition, your close contacts should be vaccinated as appropriate. Discuss appropriate individual recommendations with your doctor.

Children

Comirnaty Omicron XBB.1.5 30 micrograms/dose dispersion for injection is not recommended for children aged under 12 years.

There are paediatric formulations available for infants aged 6 months and above and children below 12 years of age. For details, please refer to the Package Leaflet for other formulations.

The vaccine is not recommended for infants aged under 6 months.

Other medicines and Comirnaty Omicron XBB.1.5

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines or have recently received any other vaccine.

Pregnancy and breast-feeding

If you are pregnant or think you may be pregnant, tell your doctor, nurse or pharmacist before you receive this vaccine.

No data are available yet regarding the use of Comirnaty Omicron XBB.1.5 during pregnancy. However, a large amount of information from pregnant women vaccinated with the initially approved Comirnaty vaccine during the second and third trimester have not shown negative effects on the pregnancy or the newborn baby. While information on effects on pregnancy or the newborn baby after vaccination during the first trimester is limited, no change to the risk for miscarriage has been seen. Comirnaty Omicron XBB.1.5 can be used during pregnancy.

No data are available yet regarding the use of Comirnaty Omicron XBB.1.5 during breast-feeding. However, no effects on the breastfed newborn/infant are anticipated. Data from women who were breast-feeding after vaccination with the initially approved Comirnaty vaccine have not shown a risk for adverse effects in breastfed newborns/infants. Comirnaty Omicron XBB.1.5 can be used while breast-feeding.

Driving and using machines

Some of the effects of vaccination mentioned in section 4 (Possible side effects) may temporarily affect your ability to drive or use machines. Wait until these effects have worn off before you drive or use machines.

3. How Comirnaty Omicron XBB.1.5 is given

Comirnaty Omicron XBB.1.5 is given as an injection of 0.3 mL into a muscle of your upper arm.

You will receive 1 injection, regardless whether you have received a COVID-19 vaccine before.

If you were previously vaccinated with a COVID-19 vaccine, you should not receive a dose of Comirnaty Omicron XBB.1.5 until at least 3 months after the most recent dose.

If you are immunocompromised, you may receive additional doses of Comirnaty Omicron XBB.1.5.

If you have any further questions on the use of Comirnaty Omicron XBB.1.5, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all vaccines, Comirnaty Omicron XBB.1.5 can cause side effects, although not everybody gets them.

Very common side effects: may affect more than 1 in 10 people

- injection site: pain, swelling
- tiredness, headache
- muscle pain, joint pain
- chills, fever
- diarrhoea

Some of these side effects were slightly more frequent in adolescents 12 to 15 years than in adults.

Common side effects: may affect up to 1 in 10 people

- injection site redness
- nausea, vomiting
- enlarged lymph nodes (more frequently observed after a booster dose)

Uncommon side effects: may affect up to 1 in 100 people

- feeling unwell, feeling weak or lack of energy/sleepy
- arm pain
- insomnia
- injection site itching
- allergic reactions such as rash or itching
- decreased appetite
- dizziness
- excessive sweating, night sweats

Rare side effects: may affect up to 1 in 1 000 people

- temporary one sided facial drooping
- allergic reactions such as hives or swelling of the face

Very rare side effects: may affect up to 1 in 10 000 people

- inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain

Not known (cannot be estimated from the available data)

- severe allergic reaction
- extensive swelling of the vaccinated limb
- swelling of the face (swelling of the face may occur in patients who have had facial dermatological fillers)
- a skin reaction that causes red spots or patches on the skin, that may look like a target or “bulls-eye” with a dark red centre surrounded by paler red rings (erythema multiforme)
- unusual feeling in the skin, such as tingling or a crawling feeling (paraesthesia)
- decreased feeling or sensitivity, especially in the skin (hypoesthesia)
- heavy menstrual bleeding (most cases appeared to be non-serious and temporary in nature)

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system](#) listed in [Appendix V](#) and include batch/Lot number if available. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Comirnaty Omicron XBB.1.5

Keep this medicine out of the sight and reach of children.

The following information about storage, expiry and use and handling is intended for healthcare professionals.

Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.

Store in freezer at -90 °C to -60 °C.

Store in the original package in order to protect from light.

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.

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 or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Multidose vials: 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 6 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed vials: Once removed from the freezer, the unopened vial may be stored and transported refrigerated at 2 °C to 8 °C for up to 10 weeks; not exceeding the printed expiry date (EXP). The outer carton should be marked with the new discard date at 2 °C to 8 °C. Once thawed, the vaccine cannot be re-frozen.

Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between 8 °C and 30 °C.

Thawed vials can be handled in room light conditions.

Opened vials: After first puncture, store the vaccine at 2 °C to 30 °C and use within 12 hours, which includes up to 6 hours transportation time. Discard any unused vaccine.

Do not use this vaccine if you notice particulates or discolouration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Comirnaty Omicron XBB.1.5 contains

- The active substance of COVID-19 mRNA Vaccine (nucleoside modified) is called raxtozinameran.
 - A single dose vial contains 1 dose of 0.3 mL with 30 micrograms raxtozinameran each.
 - A multidose vial contains 6 doses of 0.3 mL with 30 micrograms raxtozinameran each.
- The other ingredients are:
 - ((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

What Comirnaty Omicron XBB.1.5 looks like and contents of the pack

The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9) provided in either:

- A single dose vial of 1 dose in a 2 mL clear vial (type I glass), with a rubber stopper and a grey flip-off plastic cap with aluminium seal; or
- A multidose vial of 6 doses in a 2 mL clear vial (type I glass), with a rubber stopper and a grey flip-off plastic cap with aluminium seal.

Single dose vial pack size: 10 vials

Multidose vial pack sizes: 10 vials or 195 vials

Not all pack sizes may be marketed.

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- **Hrvatska:** Pfizer Croatia d.o.o., Tel: +385 1 3908 777
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URL: www.comirnatyglobal.com

Detailed information on this medicine is available on the European Medicines Agency website:
<http://www.ema.europa.eu>

The following information is intended for healthcare professionals only:

Administer Comirnaty Omicron XBB.1.5 intramuscularly as a single dose of 0.3 mL regardless of prior COVID-19 vaccination status.

For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty Omicron XBB.1.5 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Additional doses may be given to individuals who are severely immunocompromised.

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.

Handling instructions prior to use

Comirnaty Omicron XBB.1.5 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- **Verify** that the vial has a **grey plastic cap** and the product **name is Comirnaty Omicron XBB.1.5 (30 micrograms)/dose dispersion for injection** (12 years and older).
- If the vial has another product name on the label, please make reference to the Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw. Ensure vials are completely thawed prior to use.
 - 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).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Preparation of 0.3 mL doses

- Gently mix by inverting vials 10 times prior to use. Do not shake.
- Prior to mixing, the thawed dispersion may contain white to off-white opaque amorphous particles.
- After mixing, the vaccine should present as a white to off-white 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 Omicron XBB.1.5.

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 vial. Discard any unused vaccine 12 hours after first puncture.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Package leaflet: Information for the user

Comirnaty Omicron XBB.1.5 10 micrograms/dose concentrate for dispersion for injection Children 5 to 11 years COVID-19 mRNA Vaccine raxtozinameran

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects your child may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before your child receives this vaccine because it contains important information for your child.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your child's doctor, pharmacist or nurse.
- If your child gets any side effects, talk to your child's doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Comirnaty Omicron XBB.1.5 is and what it is used for
2. What you need to know before your child receives Comirnaty Omicron XBB.1.5
3. How Comirnaty Omicron XBB.1.5 is given
4. Possible side effects
5. How to store Comirnaty Omicron XBB.1.5
6. Contents of the pack and other information

1. What Comirnaty Omicron XBB.1.5 is and what it is used for

Comirnaty Omicron XBB.1.5 is a vaccine used for preventing COVID-19 caused by SARS-CoV-2.

Comirnaty Omicron XBB.1.5 10 micrograms/dose concentrate for dispersion for injection is given to children from 5 to 11 years of age.

The vaccine causes the immune system (the body's natural defences) to produce antibodies and blood cells that work against the virus, so giving protection against COVID-19.

As Comirnaty Omicron XBB.1.5 does not contain the virus to produce immunity, it cannot give your child COVID-19.

The use of this vaccine should be in accordance with official recommendations.

2. What you need to know before your child receives Comirnaty Omicron XBB.1.5

Comirnaty Omicron XBB.1.5 should not be given

- if your child is allergic to the active substance or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions

Talk to your child's doctor, pharmacist or nurse before your child is given the vaccine if your child:

- has ever had a severe allergic reaction or breathing problems after any other vaccine injection or after having been given this vaccine in the past.
- is feeling nervous about the vaccination process or has ever fainted following any needle injection.

- has a severe illness or infection with high fever. However, your child can have the vaccination if he/she has a mild fever or upper airway infection like a cold.
- has a bleeding problem, bruises easily or uses a medicine to prevent blood-clots.
- has a weakened immune system, because of a disease such as HIV infection or a medicine such as corticosteroid that affects the immune system.

There is an increased risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) after vaccination with Comirnaty (see section 4). 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. The risk of myocarditis and pericarditis seems lower in children ages 5 to 11 years compared with ages 12 to 17 years. Most cases of myocarditis and pericarditis recover. Some cases required intensive care support and fatal cases have been seen. Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

As with any vaccine, Comirnaty Omicron XBB.1.5 may not fully protect all those who receive it and it is not known how long your child will be protected.

The efficacy of Comirnaty Omicron XBB.1.5 may be lower in people who are immunocompromised. If your child is immunocompromised, he/she may receive additional doses of Comirnaty Omicron XBB.1.5. In these cases, your child should continue to maintain physical precautions to help prevent COVID-19. In addition, your child's close contacts should be vaccinated as appropriate. Discuss appropriate individual recommendations with your child's doctor.

Children

Comirnaty Omicron XBB.1.5 10 micrograms/dose concentrate for dispersion for injection is not recommended for children aged under 5 years.

There are paediatric formulations available for infants and children aged 6 months to 4 years. For details, please refer to the Package Leaflet for other formulations.

The vaccine is not recommended for infants aged under 6 months.

Other medicines and Comirnaty Omicron XBB.1.5

Tell your child's doctor or pharmacist if your child is using, has recently used or might use any other medicines or has recently received any other vaccine.

Pregnancy and breast-feeding

If your child is pregnant, tell your child's doctor, nurse or pharmacist before your child receives this vaccine.

No data are available yet regarding the use of Comirnaty Omicron XBB.1.5 during pregnancy. However, a large amount of information from pregnant women vaccinated with the initially approved Comirnaty vaccine during the second and third trimester have not shown negative effects on the pregnancy or the newborn baby. While information on effects on pregnancy or the newborn baby after vaccination during the first trimester is limited, no change to the risk for miscarriage has been seen. Comirnaty Omicron XBB.1.5 can be used during pregnancy.

No data are available yet regarding the use of Comirnaty Omicron XBB.1.5 during breast-feeding. However, no effects on the breastfed newborn/infant are anticipated. Data from women who were breast-feeding after vaccination with the initially approved Comirnaty vaccine have not shown a risk for adverse effects in breastfed newborns/infants. Comirnaty Omicron XBB.1.5 can be used while breast-feeding.

Driving and using machines

Some of the effects of vaccination mentioned in section 4 (Possible side effects) may temporarily affect your child's ability to use machines or undertake activities such as cycling. Wait until these effects have worn off before resuming activities that require your child's full attention.

3. How Comirnaty Omicron XBB.1.5 is given

Comirnaty Omicron XBB.1.5 is given after dilution as an injection of 0.2 mL into a muscle of your child's upper arm.

Your child will receive 1 injection, regardless whether he/she has received a COVID-19 vaccine before.

If your child was previously vaccinated with a COVID-19 vaccine, he/she should not receive a dose of Comirnaty Omicron XBB.1.5 until at least 3 months after the most recent dose.

If your child is immunocompromised, he/she may receive additional doses of Comirnaty Omicron XBB.1.5.

If you have any further questions on the use of Comirnaty Omicron XBB.1.5, ask your child's doctor, pharmacist or nurse.

4. Possible side effects

Like all vaccines, Comirnaty Omicron XBB.1.5 can cause side effects, although not everybody gets them.

Very common side effects: may affect more than 1 in 10 people

- injection site: pain, swelling
- tiredness, headache
- muscle pain, joint pain
- chills, fever
- diarrhoea

Common side effects: may affect up to 1 in 10 people

- nausea, vomiting
- injection site redness ('very common' in 5 to 11 years of age)
- enlarged lymph nodes (more frequently observed after a booster dose)

Uncommon side effects: may affect up to 1 in 100 people

- feeling unwell, feeling weak or lack of energy/sleepy
- arm pain
- insomnia
- injection site itching
- allergic reactions such as rash or itching
- decreased appetite
- dizziness
- excessive sweating, night sweats

Rare side effects: may affect up to 1 in 1 000 people

- temporary one sided facial drooping
- allergic reactions such as hives or swelling of the face

Very rare side effects: may affect up to 1 in 10 000 people

- inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain

Not known (cannot be estimated from the available data)

- severe allergic reaction
- extensive swelling of the vaccinated limb
- swelling of the face (swelling of the face may occur in patients who have had facial dermatological fillers)
- a skin reaction that causes red spots or patches on the skin, that may look like a target or “bulls-eye” with a dark red centre surrounded by paler red rings (erythema multiforme)
- unusual feeling in the skin, such as tingling or a crawling feeling (paraesthesia)
- decreased feeling or sensitivity, especially in the skin (hypoesthesia)
- heavy menstrual bleeding (most cases appeared to be non-serious and temporary in nature)

Reporting of side effects

If your child gets any side effects, talk to your child’s doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system](#) listed in [Appendix V](#) and include batch/Lot number if available. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Comirnaty Omicron XBB.1.5

Keep this medicine out of the sight and reach of children.

The following information about storage, expiry and use and handling is intended for healthcare professionals.

Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.

Store in freezer at -90 °C to -60 °C.

Store in the original package in order to protect from light.

The vaccine will be received frozen at -90 °C to -60 °C. Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

When stored frozen at -90 °C to -60 °C, 10-vial packs of the vaccine can be thawed at 2 °C to 8 °C for 4 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Once removed from the freezer, the unopened vial may be stored and transported refrigerated at 2 °C to 8 °C for up to 10 weeks; not exceeding the printed expiry date (EXP). The outer carton should be marked with the new discard date at 2 °C to 8 °C. Once thawed, the vaccine cannot be re-frozen.

Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between 8 °C and 30 °C.

Thawed vials can be handled in room light conditions.

After dilution, store the vaccine at 2 °C to 30 °C and use within 12 hours, which includes up to 6 hours transportation time. Discard any unused vaccine.

Do not use this vaccine if you notice particulates in the dilution or discolouration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Comirnaty Omicron XBB.1.5 contains

- The active substance of COVID-19 mRNA Vaccine (nucleoside modified) is called raxtozinameran. After dilution, the vial contains 10 doses of 0.2 mL with 10 micrograms raxtozinameran each.
- The other ingredients are:
 - ((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

What Comirnaty Omicron XBB.1.5 looks like and contents of the pack

The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9) provided in a multidose vial of 10 doses in a 2 mL clear vial (type I glass), with a rubber stopper and an orange flip-off plastic cap with aluminium seal.

Pack sizes: 10 vials or 195 vials
Not all pack sizes may be marketed.

Marketing Authorisation Holder

BioNTech Manufacturing GmbH
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55131 Mainz
Germany
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Fax: +49 6131 9084-2121
service@biontech.de

Manufacturers

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Kupferbergterrasse 17 - 19
55116 Mainz
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Pfizer Manufacturing Belgium NV
Rijksweg 12
Puurs-Sint-Amands, 2870
Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

- **België/Belgique/Belgien, Luxembourg/Luxemburg:** Pfizer S.A./N.V.,
Tél/Tel: +32 (0)2 554 62 11
- **България:** Пфайзер Люксембург САРЛ, Клон, България, Тел: +359 2 970 4333
- **Česká republika:** Pfizer, spol. s r.o., Tel: +420 283 004 111
- **Danmark:** Pfizer ApS, Tlf: +45 44 201 100
- **Deutschland:** BioNTech Manufacturing GmbH, Tel: +49 6131 90840

- **Eesti:** Pfizer Luxembourg SARL Eesti filiaal, Tel: +372 666 7500
- **Ελλάδα:** Pfizer Ελλάς Α.Ε., Τηλ.: +30 210 6785 800
- **España:** Pfizer, S.L., Tel: +34914909900
- **France:** Pfizer, Tél +33 1 58 07 34 40
- **Hrvatska:** Pfizer Croatia d.o.o., Tel: +385 1 3908 777
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- **Ísland:** Icepharma hf, Simi: +354 540 8000
- **Italia:** Pfizer S.r.l., Tel: +39 06 33 18 21
- **Κύπρος:** Pfizer Ελλάς Α.Ε. (Cyprus Branch), Τηλ: +357 22 817690
- **Latvija:** Pfizer Luxembourg SARL filiāle Latvijā, Tel.: +371 670 35 775
- **Lietuva:** Pfizer Luxembourg SARL filialas Lietuvoje, Tel. +370 52 51 4000
- **Magyarország:** Pfizer Kft, Tel: +36 1 488 3700
- **Malta:** Vivian Corporation Ltd., Tel: +35621 344610
- **Norge:** Pfizer AS, Tlf: +47 67 526 100
- **Nederland:** Pfizer BV, Tel: +31 (0)10 406 43 01
- **Österreich:** Pfizer Corporation Austria Ges.m.b.H, Tel: +43 (0)1 521 15-0
- **Polska:** Pfizer Polska Sp. z o.o., Tel.: +48 22 335 61 00
- **Portugal:** Laboratórios Pfizer, Lda., Tel: +351 21 423 5500
- **România:** Pfizer Romania S.R.L, Tel: +40 (0) 21 207 28 00
- **Slovenija:** Pfizer Luxembourg SARL, Pfizer, podružnica za svetovanje s področja farmacevtske dejavnosti, Ljubljana, Tel.: +386 (0) 1 52 11 400
- **Slovenská republika:** Pfizer Luxembourg SARL, organizačná zložka, Tel: +421 2 3355 5500
- **Suomi/Finland:** Pfizer Oy, Puh/Tel: +358 (0)9 430 040
- **Sverige:** Pfizer AB, Tel: +46 (0)8 550 520 00
- **United Kingdom (Northern Ireland):** Pfizer Limited, Tel: +44 (0) 1304 616161

This leaflet was last revised in

Scan the code with a mobile device to get the package leaflet in different languages.



URL: www.comirnatyglobal.com

Detailed information on this medicine is available on the European Medicines Agency website:
<http://www.ema.europa.eu>

The following information is intended for healthcare professionals only:

Administer Comirnaty Omicron XBB.1.5 intramuscularly after dilution as a single dose of 0.2 mL regardless of prior COVID-19 vaccination status.

For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty Omicron XBB.1.5 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Additional doses may be given to individuals who are severely immunocompromised.

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.

Handling instructions prior to use

Comirnaty Omicron XBB.1.5 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- **Verify** that the vial has an **orange plastic cap** and the product **name is Comirnaty Omicron XBB.1.5 (10 micrograms)/dose concentrate for dispersion for injection** (children 5 to 11 years).
- If the vial has another product name on the label, please make reference to the Summary of Product Characteristics 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 4 hours to thaw. Ensure vials are completely thawed prior to use.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Dilution

- 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 **1.3 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 1.3 mL air into the empty diluent syringe.
- Gently invert the diluted dispersion 10 times. Do not shake.
- The diluted vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discolouration are present.
- The diluted vials should be marked with the appropriate **discard date and time**.
- **After dilution**, store at 2 °C to 30 °C and use within **12 hours**.
- Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.

Preparation of 0.2 ml doses

- 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 Omicron XBB.1.5 for children aged 5 to 11 years. **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 12 hours after dilution.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Package leaflet: Information for the user

Comirnaty Omicron XBB.1.5 10 micrograms/dose dispersion for injection Children 5 to 11 years COVID-19 mRNA Vaccine raxtozinameran

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects your child may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before your child receives this vaccine because it contains important information for your child.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your child's doctor, pharmacist or nurse.
- If your child gets any side effects, talk to your child's doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Comirnaty Omicron XBB.1.5 is and what it is used for
2. What you need to know before your child receives Comirnaty Omicron XBB.1.5
3. How Comirnaty Omicron XBB.1.5 is given
4. Possible side effects
5. How to store Comirnaty Omicron XBB.1.5
6. Contents of the pack and other information

1. What Comirnaty Omicron XBB.1.5 is and what it is used for

Comirnaty Omicron XBB.1.5 is a vaccine used for preventing COVID-19 caused by SARS-CoV-2.

Comirnaty Omicron XBB.1.5 10 micrograms/dose dispersion for injection is given to children from 5 to 11 years of age.

The vaccine causes the immune system (the body's natural defences) to produce antibodies and blood cells that work against the virus, so giving protection against COVID-19.

As Comirnaty Omicron XBB.1.5 does not contain the virus to produce immunity, it cannot give your child COVID-19.

The use of this vaccine should be in accordance with official recommendations.

2. What you need to know before your child receives Comirnaty Omicron XBB.1.5

Comirnaty Omicron XBB.1.5 should not be given

- if your child is allergic to the active substance or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions

Talk to your child's doctor, pharmacist or nurse before your child is given the vaccine if your child:

- has ever had a severe allergic reaction or breathing problems after any other vaccine injection or after having been given this vaccine in the past.
- is feeling nervous about the vaccination process or has ever fainted following any needle injection.

- has a severe illness or infection with high fever. However, your child can have the vaccination if he/she has a mild fever or upper airway infection like a cold.
- has a bleeding problem, bruises easily or uses a medicine to prevent blood-clots.
- has a weakened immune system, because of a disease such as HIV infection or a medicine such as corticosteroid that affects the immune system.

There is an increased risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) after vaccination with Comirnaty (see section 4). 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. The risk of myocarditis and pericarditis seems lower in children ages 5 to 11 years compared with ages 12 to 17 years. Most cases of myocarditis and pericarditis recover. Some cases required intensive care support and fatal cases have been seen. Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

As with any vaccine, Comirnaty Omicron XBB.1.5 may not fully protect all those who receive it and it is not known how long your child will be protected.

The efficacy of Comirnaty Omicron XBB.1.5 may be lower in people who are immunocompromised. If your child is immunocompromised, he/she may receive additional doses of Comirnaty Omicron XBB.1.5. In these cases, your child should continue to maintain physical precautions to help prevent COVID-19. In addition, your child's close contacts should be vaccinated as appropriate. Discuss appropriate individual recommendations with your child's doctor.

Children

Comirnaty Omicron XBB.1.5 10 micrograms/dose dispersion for injection is not recommended for children aged under 5 years.

There are paediatric formulations available for infants and children aged 6 months to 4 years. For details, please refer to the Package Leaflet for other formulations.

The vaccine is not recommended for infants aged under 6 months.

Other medicines and Comirnaty Omicron XBB.1.5

Tell your child's doctor or pharmacist if your child is using, has recently used or might use any other medicines or has recently received any other vaccine.

Pregnancy and breast-feeding

If your child is pregnant, tell your child's doctor, nurse or pharmacist before your child receives this vaccine.

No data are available yet regarding the use of Comirnaty Omicron XBB.1.5 during pregnancy. However, a large amount of information from pregnant women vaccinated with the initially approved Comirnaty vaccine during the second and third trimester have not shown negative effects on the pregnancy or the newborn baby. While information on effects on pregnancy or the newborn baby after vaccination during the first trimester is limited, no change to the risk for miscarriage has been seen. Comirnaty Omicron XBB.1.5 can be used during pregnancy.

No data are available yet regarding the use of Comirnaty Omicron XBB.1.5 during breast-feeding. However, no effects on the breastfed newborn/infant are anticipated. Data from women who were breast-feeding after vaccination with the initially approved Comirnaty vaccine have not shown a risk for adverse effects in breastfed newborns/infants. Comirnaty Omicron XBB.1.5 can be used while breast-feeding.

Driving and using machines

Some of the effects of vaccination mentioned in section 4 (Possible side effects) may temporarily affect your child's ability to use machines or undertake activities such as cycling. Wait until these effects have worn off before resuming activities that require your child's full attention.

3. How Comirnaty Omicron XBB.1.5 is given

Comirnaty Omicron XBB.1.5 is given as an injection of 0.3 mL into a muscle of your child's upper arm.

Your child will receive 1 injection, regardless whether he/she has received a COVID-19 vaccine before.

If your child was previously vaccinated with a COVID-19 vaccine, he/she should not receive a dose of Comirnaty Omicron XBB.1.5 until at least 3 months after the most recent dose.

If your child is immunocompromised, he/she may receive additional doses of Comirnaty Omicron XBB.1.5.

If you have any further questions on the use of Comirnaty Omicron XBB.1.5, ask your child's doctor, pharmacist or nurse.

4. Possible side effects

Like all vaccines, Comirnaty Omicron XBB.1.5 can cause side effects, although not everybody gets them.

Very common side effects: may affect more than 1 in 10 people

- injection site: pain, swelling
- tiredness, headache
- muscle pain, joint pain
- chills, fever
- diarrhoea

Common side effects: may affect up to 1 in 10 people

- nausea, vomiting
- injection site redness ('very common' in 5 to 11 years of age)
- enlarged lymph nodes (more frequently observed after a booster dose)

Uncommon side effects: may affect up to 1 in 100 people

- feeling unwell, feeling weak or lack of energy/sleepy
- arm pain
- insomnia
- injection site itching
- allergic reactions such as rash or itching
- decreased appetite
- dizziness
- excessive sweating, night sweats

Rare side effects: may affect up to 1 in 1 000 people

- temporary one sided facial drooping
- allergic reactions such as hives or swelling of the face

Very rare side effects: may affect up to 1 in 10 000 people

- inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain

Not known (cannot be estimated from the available data)

- severe allergic reaction
- extensive swelling of the vaccinated limb
- swelling of the face (swelling of the face may occur in patients who have had facial dermatological fillers)
- a skin reaction that causes red spots or patches on the skin, that may look like a target or “bulls-eye” with a dark red centre surrounded by paler red rings (erythema multiforme)
- unusual feeling in the skin, such as tingling or a crawling feeling (paraesthesia)
- decreased feeling or sensitivity, especially in the skin (hypoesthesia)
- heavy menstrual bleeding (most cases appeared to be non-serious and temporary in nature)

Reporting of side effects

If your child gets any side effects, talk to your child’s doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system](#) listed in [Appendix V](#) and include batch/Lot number if available. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Comirnaty Omicron XBB.1.5

Keep this medicine out of the sight and reach of children.

The following information about storage, expiry and use and handling is intended for healthcare professionals.

Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.

Store in freezer at -90 °C to -60 °C.

Store in the original package in order to protect from light.

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.

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 or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Multidose vials: 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 6 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed vials: Once removed from the freezer, the unopened vial may be stored and transported refrigerated at 2 °C to 8 °C for up to 10 weeks; not exceeding the printed expiry date (EXP). The outer carton should be marked with the new discard date at 2 °C to 8 °C. Once thawed, the vaccine cannot be re-frozen.

Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between 8 °C and 30 °C.

Thawed vials can be handled in room light conditions.

Opened vials: After first puncture, store the vaccine at 2 °C to 30 °C and use within 12 hours, which includes up to 6 hours transportation time. Discard any unused vaccine.

Do not use this vaccine if you notice particulates or discolouration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Comirnaty Omicron XBB.1.5 contains

- The active substance of COVID-19 mRNA Vaccine (nucleoside modified) is called raxtozinameran.
 - A single dose vial contains 1 dose of 0.3 mL with 10 micrograms of raxtozinameran per dose.
 - A multidose vial contains 6 doses of 0.3 mL with 10 micrograms of raxtozinameran per dose.
- The other ingredients are:
 - ((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

What Comirnaty Omicron XBB.1.5 looks like and contents of the pack

The vaccine is a clear to slightly opalescent dispersion (pH: 6.9 - 7.9) provided in either:

- A single dose vial of 1 dose in a 2 mL clear vial (type I glass), with a rubber stopper and a blue flip-off plastic cap with aluminium seal; or
- A multidose vial of 6 doses in a 2 mL clear vial (type I glass), with a rubber stopper and a blue flip-off plastic cap with aluminium seal.

Single dose vial pack size: 10 vials

Multidose vial pack size: 10 vials

Not all pack sizes may be marketed.

Marketing Authorisation Holder

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- **România:** Pfizer Romania S.R.L, Tel: +40 (0) 21 207 28 00
- **Slovenija:** Pfizer Luxembourg SARL, Pfizer, podružnica za svetovanje s področja farmacevtske dejavnosti, Ljubljana, Tel.: +386 (0) 1 52 11 400
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- **United Kingdom (Northern Ireland):** Pfizer Limited, Tel: +44 (0) 1304 616161

This leaflet was last revised in

Scan the code with a mobile device to get the package leaflet in different languages.



URL: www.comirnatyglobal.com

Detailed information on this medicine is available on the European Medicines Agency website:
<http://www.ema.europa.eu>

The following information is intended for healthcare professionals only:

Administer Comirnaty Omicron XBB.1.5 intramuscularly as a single dose of 0.3 mL regardless of prior COVID-19 vaccination status.

For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty Omicron XBB.1.5 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Additional doses may be given to individuals who are severely immunocompromised.

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.

Handling instructions prior to use

Comirnaty Omicron XBB.1.5 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- **Verify** that the vial has a **blue plastic cap** and the product **name is Comirnaty Omicron XBB.1.5 (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 Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw. Ensure vials are completely thawed prior to use.
 - 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).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Preparation of 0.3 mL doses

- Gently mix by inverting vials 10 times prior to use. Do not shake.
- Prior to mixing, the thawed dispersion may contain white to off-white opaque amorphous particles.
- After mixing, the vaccine should present as a clear to slightly opalescent dispersion with no particulates visible. Do not use the vaccine if particulates or discolouration are present.
- 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 Omicron XBB.1.5 for children aged 5 to 11 years.

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 vial. Discard any unused vaccine 12 hours after first puncture.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Package leaflet: Information for the user

Comirnaty Omicron XBB.1.5 3 micrograms/dose concentrate for dispersion for injection Infants and children 6 months to 4 years COVID-19 mRNA Vaccine raxtozinameran

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects your child may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before your child receives this vaccine because it contains important information for your child.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your child's doctor, pharmacist or nurse.
- If your child gets any side effects, talk to your child's doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Comirnaty Omicron XBB.1.5 is and what it is used for
2. What you need to know before your child receives Comirnaty Omicron XBB.1.5
3. How Comirnaty Omicron XBB.1.5 is given
4. Possible side effects
5. How to store Comirnaty Omicron XBB.1.5
6. Contents of the pack and other information

1. What Comirnaty Omicron XBB.1.5 is and what it is used for

Comirnaty Omicron XBB.1.5 is a vaccine used for preventing COVID-19 caused by SARS-CoV-2.

Comirnaty Omicron XBB.1.5 3 micrograms/dose concentrate for dispersion for injection is given to infants and children from 6 months to 4 years of age.

The vaccine causes the immune system (the body's natural defences) to produce antibodies and blood cells that work against the virus, so giving protection against COVID-19.

As Comirnaty Omicron XBB.1.5 does not contain the virus to produce immunity, it cannot give your child COVID-19.

The use of this vaccine should be in accordance with official recommendations.

2. What you need to know before your child receives Comirnaty Omicron XBB.1.5

Comirnaty Omicron XBB.1.5 should not be given

- if your child is allergic to the active substance or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions

Talk to your child's doctor, pharmacist or nurse before your child is given the vaccine if your child:

- has ever had a severe allergic reaction or breathing problems after any other vaccine injection or after having been given this vaccine in the past.
- is feeling nervous about the vaccination process or has ever fainted following any needle injection.

- has a severe illness or infection with high fever. However, your child can have the vaccination if he/she has a mild fever or upper airway infection like a cold.
- has a bleeding problem, bruises easily or uses a medicine to prevent blood-clots.
- has a weakened immune system, because of a disease such as HIV infection or a medicine such as corticosteroid that affects the immune system.

There is an increased risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) after vaccination with Comirnaty (see section 4). 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. The risk of myocarditis and pericarditis seems lower in children ages 5 to 11 years compared with ages 12 to 17 years. Most cases of myocarditis and pericarditis recover. Some cases required intensive care support and fatal cases have been seen. Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

As with any vaccine, Comirnaty Omicron XBB.1.5 may not fully protect all those who receive it and it is not known how long your child will be protected.

The efficacy of Comirnaty may be lower in people who are immunocompromised. If your child is immunocompromised, he/she may receive additional doses of Comirnaty. In these cases, your child should continue to maintain physical precautions to help prevent COVID-19. In addition, your child's close contacts should be vaccinated as appropriate. Discuss appropriate individual recommendations with your child's doctor.

Children

Comirnaty Omicron XBB.1.5 3 micrograms/dose concentrate for dispersion for injection is not recommended for children aged 5 years to 11 years.

There are paediatric formulations available for children 5 to 11 years of age. For details, please refer to the Package Leaflet for other formulations.

The vaccine is not recommended for infants aged under 6 months.

Other medicines and Comirnaty Omicron XBB.1.5

Tell your child's doctor or pharmacist if your child is using, has recently used or might use any other medicines or has recently received any other vaccine.

Pregnancy and breast-feeding

Comirnaty Omicron XBB.1.5 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 Package Leaflet for those formulations.

Driving and using machines

Some of the effects of vaccination mentioned in section 4 (Possible side effects) may temporarily affect your child's ability to use machines or undertake activities such as cycling. Wait until these effects have worn off before resuming activities that require your child's full attention.

3. How Comirnaty Omicron XBB.1.5 is given

If your infant is from 6 months to less than 12 months of age, he/she will be given Comirnaty Omicron XBB.1.5 after dilution as an injection of 0.2 mL into a muscle of the thigh. If your infant or child is 1 year of age or older, he/she will be given Comirnaty Omicron XBB.1.5 after dilution as an injection of 0.2 mL into a muscle of the thigh or into a muscle of the upper arm.

If your child has not completed a COVID-19 primary vaccination course or has not been infected by COVID-19 in the past, your child will receive a maximum of 3 injections (the total number of doses required as primary course). It is recommended to receive the second dose 3 weeks after the first dose followed by a third dose at least 8 weeks after the second dose to complete the primary course.

If your child has previously completed a COVID-19 primary vaccination course or has had COVID-19, your child will receive 1 injection. If your child was previously vaccinated with a COVID-19 vaccine, your child should not receive a dose of Comirnaty Omicron XBB.1.5 until at least 3 months after the most recent dose.

If your 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.

If your child is immunocompromised, he/she may receive additional doses of Comirnaty Omicron XBB.1.5.

Interchangeability

Your child may receive either Comirnaty, Comirnaty Original/Omicron BA.4-5, or Comirnaty Omicron XBB.1.5 (or a combination) for the primary course. Your child should not receive more than the total number of doses needed as primary course. Your child should only be administered the primary course once.

If you have any further questions on the use of Comirnaty Omicron XBB.1.5, ask your child's doctor, pharmacist or nurse.

4. Possible side effects

Like all vaccines, Comirnaty Omicron XBB.1.5 can cause side effects, although not everybody gets them.

Very common side effects: may affect more than 1 in 10 people

- irritability (6 months to < 2 years)
- injection site: pain/tenderness, swelling
- tiredness, headache
- drowsiness (6 months to < 2 years)
- muscle pain, joint pain
- chills, fever
- diarrhoea

Common side effects: may affect up to 1 in 10 people

- nausea, vomiting
- injection site redness ('very common' in 6 months to 11 years)
- enlarged lymph nodes (more frequently observed after a booster dose)

Uncommon side effects: may affect up to 1 in 100 people

- feeling unwell, feeling weak or lack of energy/sleepy
- arm pain
- insomnia
- injection site itching
- allergic reactions such as rash ('common' for 6 months to < 2 years) or itching
- decreased appetite ('very common' for 6 months to < 2 years)
- dizziness
- excessive sweating, night sweats

Rare side effects: may affect up to 1 in 1 000 people

- temporary one sided facial drooping
- allergic reactions such as hives or swelling of the face

Very rare side effects: may affect up to 1 in 10 000 people

- inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain

Not known (cannot be estimated from the available data)

- severe allergic reaction
- extensive swelling of the vaccinated limb
- swelling of the face (swelling of the face may occur in patients who have had facial dermatological fillers)
- a skin reaction that causes red spots or patches on the skin, that may look like a target or “bulls-eye” with a dark red centre surrounded by paler red rings (erythema multiforme)
- unusual feeling in the skin, such as tingling or a crawling feeling (paraesthesia)
- decreased feeling or sensitivity, especially in the skin (hypoesthesia)
- heavy menstrual bleeding (most cases appeared to be non-serious and temporary in nature)

Reporting of side effects

If your child gets any side effects, talk to your child’s doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system](#) listed in [Appendix V](#) and include batch/Lot number if available. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Comirnaty Omicron XBB.1.5

Keep this medicine out of the sight and reach of children.

The following information about storage, expiry and use and handling is intended for healthcare professionals.

Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.

Store in freezer at -90 °C to -60 °C.

Store in the original package in order to protect from light.

The vaccine will be received frozen at -90 °C to -60 °C. Frozen vaccine can be stored either at -90 °C to -60 °C or 2 °C to 8 °C upon receipt.

When stored frozen at -90 °C to -60 °C, 10-vial packs of the vaccine can be thawed at 2 °C to 8 °C for 2 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Once removed from the freezer, the unopened vial may be stored and transported refrigerated at 2 °C to 8 °C for up to 10 weeks; not exceeding the printed expiry date (EXP). The outer carton should be marked with the new discard date at 2 °C to 8 °C. Once thawed, the vaccine cannot be re-frozen.

Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between 8 °C and 30 °C.

Thawed vials can be handled in room light conditions.

After dilution, store the vaccine at 2 °C to 30 °C and use within 12 hours, which includes up to 6 hours transportation time. Discard any unused vaccine.

Do not use this vaccine if you notice particulates in the dilution or discolouration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Comirnaty Omicron XBB.1.5 contains

- The active substance of COVID-19 mRNA Vaccine (nucleoside modified) is called raxtozinameran. After dilution, the vial contains 10 doses of 0.2 mL with 3 micrograms raxtozinameran each.
- The other ingredients are:
 - ((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

What Comirnaty Omicron XBB.1.5 looks like and contents of the pack

The vaccine is a white to off-white dispersion (pH: 6.9 - 7.9) provided in a multidose vial of 10 doses in a 2 mL clear vial (type I glass), with a rubber stopper and a maroon flip-off plastic cap with aluminium seal.

Pack size: 10 vials

Marketing Authorisation Holder

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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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- **Česká republika:** Pfizer, spol. s r.o., Tel: +420 283 004 111
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- **Hrvatska:** Pfizer Croatia d.o.o., Tel: +385 1 3908 777
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- **Slovenská republika:** Pfizer Luxembourg SARL, organizačná zložka, Tel: +421 2 3355 5500
- **Suomi/Finland:** Pfizer Oy, Puh/Tel: +358 (0)9 430 040
- **Sverige:** Pfizer AB, Tel: +46 (0)8 550 520 00
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Detailed information on this medicine is available on the European Medicines Agency website:
<http://www.ema.europa.eu>

The following information is intended for healthcare professionals only:

If the child has not completed a COVID-19 primary vaccination course or does not have a history of prior SARS-CoV-2 infection, administer Comirnaty Omicron XBB.1.5 intramuscularly after dilution as a primary course of maximum 3 doses (the total number of doses required as primary course) (0.2 mL each); the second dose administered 3 weeks after the first dose followed by a third dose at least 8 weeks after the second dose to complete the primary course.

If the child has completed a COVID-19 primary vaccination course or has a history of prior SARS-CoV-2 infection, administer Comirnaty Omicron XBB.1.5 intramuscularly after dilution a

single dose of 0.2 mL. If the individual was previously vaccinated with a COVID-19 vaccine, the individual should receive a dose of Comirnaty Omicron XBB.1.5 at least 3 months after the most recent dose.

Additional doses may be given to individuals who are severely immunocompromised.

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.

Handling instructions prior to use

Comirnaty Omicron XBB.1.5 should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

- **Verify** that the vial has a **maroon plastic cap** and the product **name is Comirnaty Omicron XBB.1.5 (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, please make reference to the Summary of Product Characteristics for that formulation.
- If the vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 10-vial pack may take 2 hours to thaw. Ensure vials are completely thawed prior to use.
- Upon moving vials to 2 °C to 8 °C storage, update the expiry date on the carton.
- Unopened vials can be **stored for up to 10 weeks at 2 °C to 8 °C**; not exceeding the printed expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C.
- Prior to use, the unopened vial can be stored for up to 12 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions.

Dilution

- 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 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 2.2 mL air into the empty diluent syringe.
- Gently invert the diluted dispersion 10 times. Do not shake.
- The diluted vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discolouration are present.
- The diluted vials should be marked with the appropriate **discard date and time**.
- **After dilution**, store at 2 °C to 30 °C and use within **12 hours**.
- Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.

Preparation of 0.2 mL doses

- 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 Omicron XBB.1.5 for infants and children aged 6 months to 4 years.
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 12 hours after dilution.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.