▼This vaccine is subject to additional monitoring **in Australia**. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – COMIRNATY® Original/Omicron BA.4-5 COVID- 19 VACCINE

1. NAME OF THE MEDICINE

Tozinameran and Famtozinameran

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tozinameran and famtozinameran are 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 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Original and Omicron BA.4-5).

COMIRNATY Original/Omicron BA.4-5			
Age group	12 years and older	5 to <12 years	6 months to <5 years
Strength per dose	15/15 micrograms	5/5 micrograms	1.5/1.5 micrograms

Each dose contains COVID-19 mRNA Vaccine embedded in lipid nanoparticles.
For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Age group	**12 years and older**		**5 to <12 years**			**6 months to <5 years**
AUST R	413718	400874	412350	413720	413719	417266
Cap & Label colour code	Light Grey	Dark Grey	Orange	Light Blue	Dark Blue	Maroon
Pharmaceutical form	Suspension for injection		Concentrate for suspension for injection	Suspension for injection		Concentrate for suspension for injection
Strength per dose	15/15 micrograms (0.3 mL dose)		5/5 micrograms (0.2 mL dose)	5/5 micrograms (0.3 mL dose)		1.5/1.5 micrograms (0.2 mL dose)
Fill volume	0.48 mL	2.25 mL	1.3 mL	0.48 mL	2.25 mL	0.4 mL
No. of doses per vial	1	6	10	1	6	10
Dilution	Do not dilute		Requires dilution	Do not dilute		Requires dilution

COMIRNATY Original/Omicron BA.4-5 (Grey, Orange and Maroon cap) is a white to off-white frozen suspension.

COMIRNATY Original/Omicron BA.4-5 (Blue cap) is a clear to slightly opalescent solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

COMIRNATY Original/Omicron BA.4-5 Vaccine has **provisional approval** for the indication below:

Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 6 months of age and older.

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

The decision has been made on the basis of short term immunogenicity and safety data. Continued approval depends on the evidence of longer term efficacy and safety from ongoing clinical trials and post-market assessment.

4.2 Dose and method of administration

Dosage

Strength and Age of Individual	Cap and Label Color	Volume of Each Dose	Dose Schedule for Primary Series and Additional dose(s)
1.5/1.5 micrograms per dose 6 months to <5 years	Maroon	0.2 mL	**Primary series:** 3 doses Dose 1 and 2: at least 3 weeks apart Dose 3: at least 8 weeks after second dose. **Additional dose(s)**: at least 3 months after a previous dose
5/5 micrograms per dose 5 to <12 years	Orange	0.2 mL	**Primary series:** 2 doses at least to 21 days (preferably 3 weeks) apart **Additional dose(s)**: at least 3 months after a previous dose
	Blue	0.3 mL	
15/15 micrograms per dose 12 years and older	Grey	0.3 mL	

Primary series, when clinically indicated, can be given to the individuals such as those who are vaccine-naïve and immunocompromised.

The use of this vaccine should be in accordance with clinical recommendations in Australia, made by ATAGI in the Australian Immunisation Handbook.

Severely immunocompromised aged 12 years and older

In accordance with official recommendations, a third dose may be given, as part of the primary series, at least 28 days after the second dose to individuals who are severely immunocompromised (see Section 4.4 Special warnings and precautions for use).

Elderly population

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

Paediatric population

Children who will turn from 4 years to 5 years of age or from 11 years to 12 years of age between their doses in the vaccination series should receive their age-appropriate dose at the time of the vaccination and the interval between doses is determined by the individual's age at the start of the vaccination series.

Interchangeability

There are limited data on the interchangeability of COMIRNATY with other COVID-19 vaccines to complete the primary vaccination course or any subsequent doses. Individuals who have received 1 dose of COMIRNATY Original/Omicron BA.4-5 should continue to receive COMIRNATY Original/Omicron BA.4-5 to complete the primary vaccination course and for any additional doses.

Method of administration

In individuals 5 years of age and older, administer the vaccine intramuscularly in the deltoid muscle.

In individuals 1 to <5 years of age and older, administer the vaccine intramuscularly in the anterolateral aspect of the thigh or the deltoid muscle.

In individuals from 6 to <12 months of age, administer the vaccine intramuscularly in the anterolateral aspect of the thigh.

Do not inject the vaccine intravascularly, subcutaneously or intradermally.

COMIRNATY Original/Omicron BA.4-5 should not be mixed in the same syringe with any other vaccines or medicinal products.

For precautions to be taken before administering COMIRNATY Original/Omicron BA.4-5, see Section 4.4 Special warnings and precautions for use.

Handling Instructions

Handing prior to use
Frozen vials must be completely thawed prior to use. Frozen vials should be transferred to 2 °C to 8 °C to thaw. Thaw times for 10-vial packs are noted in table below:

Vial Cap Color	**Time That May Be Required For a 10-vial Pack to Thaw (at 2 °C to 8 °C)**
Light Grey Light Blue Maroon	2 hours
Orange	4 hours
Dark Grey Dark Blue	6 hours

- Upon moving frozen vaccine to 2 °C to 8 °C storage, update the expiry date on the carton. The updated expiry date should reflect 10 weeks from the date of transfer to refrigerated conditions (2 °C to 8 °C) and not exceeding the original printed expiry date (EXP).

- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C for immediate use.
- If the vaccine is received at 2 °C to 8 °C it should continue to be stored at 2 °C to 8 °C. Check that the carton has been previously updated to reflect the 10-week refrigerated expiry date.
- Unopened vials can be stored for up to 12 hours at temperatures up to 30 °C. Total storage time between 8 ºC to 30 ºC, inclusive of storage before and after puncture, should not exceed 24 hours.

COMIRNATY Original/Omicron BA.4-5 Suspension for Injection

Preparation for administration

COMIRNATY Original/Omicron BA.4-5 Suspension for Injection should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared suspension.

Vials of COMIRNATY Original/Omicron BA.4-5 Suspension for Injection have either a grey or a blue cap, contain either 1 or 6 doses of 0.3 mL of vaccine and do not require dilution.

- Light Grey or Light Blue cap: single dose vial
- Dark Grey or Dark Blue cap: 6 dose multidose vial

Vial verification

Prior to administration, check the name and strength of the vaccine on the vial label and the colour of the vial cap and vial label border to ensure it is the intended presentation. Check whether the vial is a single dose vial or a multidose vial and check if the vial requires dilution.

- Check appearance of vaccine prior to mixing and administration.
  - Grey cap vials: Prior to mixing, the vaccine is a white to off-white dispersion and may contain white to off-white opaque amorphous particles.
  - Blue cap vials: Prior to mixing, the vaccine is a clear to slightly opalescent dispersion and may contain white to off-white opaque amorphous particles.
- Gently invert the vial 10 times. **Do not shake.**
- Do not use the vaccine if particulates or discoloration are present after mixing.

Preparation of individual doses

- Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
- Withdraw a 0.3 mL single dose.
- *For Dark Grey or Dark Blue cap multidose vials (6 doses per vial):*
  - After first puncture, record appropriate date and time on the vial and store at 2 ºC to 30 ºC for up to 12 hours. Do not re-freeze.
  - Each dose must contain 0.3 mL of vaccine. Low dead-volume syringes and/or needles should be used in order to extract all doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microliters.
  - If the amount of vaccine remaining in the vial cannot provide a full dose, discard the vial and any excess volume.

COMIRNATY Original/Omicron BA.4-5 Concentrated Suspension for Injection

Preparation for administration

COMIRNATY Original/Omicron BA.4-5 Concentrated Suspension for Injection should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared diluted suspension.

Vials of COMIRNATY Original/Omicron BA.4-5 Concentrated Suspension for Injection have either an Orange or a Maroon cap, contains 10 doses of 0.2 mL of vaccine after dilution.

Vial verification

Prior to administration, check the name and strength of the vaccine on the vial label and the colour of the vial cap and vial label border to ensure it is the intended presentation. Check whether the vial is a single dose vial or a multidose vial and check if the vial requires dilution.

Prior to dilution

- After the thawed vial has reached room temperature, gently invert it 10 times prior to dilution. **Do not shake.**
- Check appearance of vaccine.
    - *Orange or Maroon cap vials:* Prior to dilution, the vaccine is a white to off-white dispersion and may contain white to off-white opaque amorphous particles.

Dilution instructions

- Thawed vaccine must be diluted in its original vial with sodium chloride 9 mg/mL (0.9%) solution for injection, using a 21 gauge or narrower needle and aseptic techniques. Volume of sodium chloride 9 mg/mL (0.9%) required are noted below:
    - *Orange cap vials:* 1.3 mL of sodium chloride 9 mg/mL
    - *Maroon cap vials:* 2.2 mL of sodium chloride 9 mg/mL
- Equalize vial pressure before removing the needle from the vial stopper by withdrawing air into the empty diluent syringe. Volume of air required are noted below:
    - *Orange cap vials:* 1.3 mL of air
    - *Maroon cap vials:* 2.2 mL of air
- Gently invert the diluted dispersion 10 times. **Do not shake.**
- Check appearance of vaccine after dilution.
    - *Orange or Maroon cap vials:* 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 discoloration are present.
- After dilution, mark vial with appropriate date/time, store at 2 ºC to 30 ºC and use within 12 hours. Do not re-freeze.

Preparation of individual doses

- Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
- Withdraw a single dose.
    - *Orange or Maroon cap multidose vials (10 doses per vial):* each dose must contain 0.2 mL of vaccine. Low dead-volume syringes and/or needles should be used in order to extract all doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microliters.
    - If the amount of vaccine remaining in the vial cannot provide a full dose, discard the vial and any excess volume.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Traceability

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

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.

The individual should be kept under close observation for at least 15 minutes following vaccination. COMIRNATY Original/Omicron BA.4-5 should not be given to those who have experienced anaphylaxis to the first dose of COMIRNATY or COMIRNATY Original/Omicron BA.4-5.

Myocarditis and pericarditis

Very rare cases of myocarditis and pericarditis have been observed following vaccination with COMIRNATY. Cases have occurred following first and second vaccinations and following booster doses. These cases have primarily occurred within 14 days following vaccination, more often after the second vaccination, and more often, but not exclusively, in younger males. There have been reports in females. Based on accumulating data, the reporting rates of myocarditis and pericarditis after primary series in children ages 5 to <12 years are lower than in ages 12 to 17 years. Rates of myocarditis and pericarditis in booster doses do not appear to be higher than after the second dose in the primary series. Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general. Cases of myocarditis and pericarditis following vaccination have rarely been associated with severe outcomes including death.

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis, including atypical presentations. Vaccinees 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. Non-specific symptoms of myocarditis and pericarditis also include fatigue, nausea and vomiting, abdominal pain, dizziness or syncope, oedema and cough. Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

For further details, please refer to the relevant clinical guidelines developed by the Australian Technical Advisory Group on Immunisation.

Anxiety-related reactions

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions may occur in association with vaccination as a psychogenic response to the needle injection. It is important that precautions are in place to avoid injury from fainting.

Some individuals may have stress-related responses associated with the process of vaccination itself. Stress-related responses are temporary and resolve on their own. They may include dizziness, fainting, palpitations, increases in heart rate, alterations in blood pressure, feeling short of breath, tingling sensations, sweating and/or anxiety. Individuals should be advised to bring symptoms to the attention of the vaccination provider for evaluation and precautions should be in place to avoid injury from fainting.

Syncope

Syncope (fainting) may occur in association with administration of injectable vaccines. Procedures should be 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, safety and immunogenicity 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 immunosuppressed individuals.

Duration of protection

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

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 completion of their primary course of the vaccine.

Use in the elderly

Clinical studies of COMIRNATY Original/Omicron BA.4-5 include participants 55 years of age and older and their data contributes to the overall assessment of safety and immunogenicity. See Section 5.1 Pharmacodynamic properties, Clinical trials, Efficacy against COVID-19. No dosage adjustment is required in elderly individuals ≥65 years of age.

The data for use in the frail elderly is limited. The potential benefits of vaccination versus the potential risk and clinical impact of even relatively mild systemic adverse events in the frail elderly should be carefully assessed on a case-by-case basis.

Paediatric use

The safety and efficacy of COMIRNATY Original/Omicron BA.4-5 in individuals aged less than 6 months of age have not yet been established.

Limited safety and effectiveness data is available for COMIRNATY (tozinameran) booster dose in adolescents 12 to 15 years of age and no immunogenicity data is available for booster dose in this age group. The safety and effectiveness of a booster dose of COMIRNATY (tozinameran) in individuals 12 to 17 years of age is based on safety and effectiveness data in adults at least 18 to 55 years of age.

Real world evidence from the Ministry of Health of Israel and surveillance by CDC in USA on the administration of third doses of COMIRNATY (tozinameran) given after the primary course revealed no new safety concerns in adolescents 12 to 17 years of age.

Very rare cases of myocarditis and pericarditis have been observed following vaccination with COMIRNATY in adolescents (see Section 4.4 Special warnings and precautions for use, Myocarditis and pericarditis).

Effects on laboratory tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

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

Effects on fertility

There are no animal reproductive toxicity studies with COMIRNATY Original/Omicron BA.4-5.

In a combined fertility and developmental toxicity study, female rats were intramuscularly administered COMIRNATY prior to mating and during gestation (4 full human doses of 30 µg each, spanning between pre-mating day 21 and gestation day 20). SARS CoV-2 neutralising antibodies were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in fetuses and offspring. There were no vaccine related effects on female fertility and pregnancy rate.

Use in pregnancy - Pregnancy Category B1

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 (tozinameran) 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.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/fetal development, parturition or post-natal development (see Section 4.6 Fertility, pregnancy and lactation, Effects on fertility). Administration of COMIRNATY Original/Omicron BA.4-5 in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and fetus.

Use in lactation

No data are available yet regarding the use of COMIRNATY Original/Omicron BA.4-5 during breast-feeding. COMIRNATY Original/Omicron BA.4-5 can be used while breast-feeding, when the potential benefits outweigh any potential risks for the mother and baby.

It is unknown whether tozinameran is excreted in human milk. A combined fertility and developmental toxicity study in rats did not show harmful effects on offspring development before weaning (see Section 4.6 Fertility, pregnancy and lactation, Effects on fertility).

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 Adverse effects (undesirable effects) may temporarily affect the ability to drive or use machines.

4.8 Adverse effects (undesirable effects)

Summary of safety profile

COMIRNATY Original/Omicron BA.4-5 (tozinameran/famtozinameran)

Participants 12 years of age and older – after bivalent Omicron BA.4-5 booster dose

In a subset from Study C4591044 (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 previously vaccinated with a 2-dose primary series and 1 booster dose of COMIRNATY (tozinameran) went on to receive a second booster dose with COMIRNATY Original/Omicron BA.4-5 (15/15 micrograms) 5.4 to 16.9 months after receiving the first booster dose and had a median follow up time of at least 1.5 months up to a data cut-off date 12 October 2022 (Cohort 2) and 31 October 2022 (Cohort 3).

The overall safety profile for the COMIRNATY Original/Omicron BA.4-5 booster (fourth dose) was similar to that seen after the COMIRNATY (tozinameran) booster (third dose). 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%). No new adverse reactions were identified for COMIRNATY Original/Omicron BA.4-5.

At present, data relating only to short term (1 month post booster) local and systemic effects are available. Long term safety data for COMIRNATY Original/Omicron BA.4-5 (tozinameran/famtozinameran) are not available.

Participants 5 to <12 years of age – after bivalent Omicron BA.4-5 booster dose

In a subset from Study C4591048 (Phase 3), 113 participants 5 to 11 years of age who had completed a 2-dose primary series and 1 booster dose of COMIRNATY (tozinameran), received a second booster dose of COMIRNATY Original/Omicron BA.4-5 (5/5 micrograms) 2.6 to 8.5 months after receiving the first booster dose. Participants who received a booster 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 was similar to that seen after 3 doses of COMIRNATY (tozinameran). The most frequent adverse reactions in participants 5 to <12 years of age were injection site pain (>60%), fatigue (>40%), headache (>20%), and muscle pain (>10%).

Participants 2 to <5 years of age – after bivalent Omicron BA.4-5 booster dose

In a subset from Study C4591048 (Phase 3), 124 participants 2 to 4 years of age who had completed a 3-dose primary series, received a booster dose of COMIRNATY Original/Omicron BA.4-5 (1.5/1.5 micrograms) 2.2 to 8.6 months after receiving Dose 3. Participants who received a booster dose of COMIRNATY Original/Omicron BA.4-5 had a median follow-up time of 1.8 months up to a data cut-off date of 30 November 2022.

The overall safety profile for the COMIRNATY Original/Omicron BA.4-5 booster was similar to that seen after 3 doses of COMIRNATY (tozinameran). The most frequent adverse reactions in participants 2 to <5 years of age were injection site pain (31.5%) and fatigue (29.3%). Pyrexia was commonly observed (4.8%).

Participants 6 months to <2 years of age – after bivalent Omicron BA.4-5 booster dose

In a subset from Study C4591048 (Phase 3), 39 participants 6 to 23 months of age who had completed a 3-dose primary series, received a booster dose of COMIRNATY Original/Omicron BA.4-5 (1.5/1.5 micrograms) 2.1 to 8.6 months after receiving Dose 3. Participants who received a booster dose of COMIRNATY Original/Omicron BA.4-5 had a median follow-up time of 1.7 months up to a data cut-off date of 30 November 2022.

The overall safety profile for the COMIRNATY Original/Omicron BA.4-5 booster was similar to that seen after 3 doses of COMIRNATY (tozinameran). The most frequent adverse reaction in participants 6 to 23 months of age were irritability (29.7%) and decreased appetite (18.9%). Pyrexia was commonly observed (5.1%).

COMIRNATY (tozinameran)

The safety of COMIRNATY (tozinameran) was evaluated in participants aged 6 months and older in clinical studies (comprised of 22,026 participants 16 years of age and older and 1,131 adolescents 12 to 15 years of age from Study C4591001, and 1,518 children 5 to <12 years of age, 1,835 participants 2 to <5 years of age and 1,178 participants 6 months to <2 years of age from Study C4591007) that have received at least one dose of COMIRNATY (tozinameran).

Additionally, 306 existing Phase 3 participants 18 to 55 years of age received a booster dose of COMIRNATY (tozinameran) approximately 6 months after the second dose in the non-placebo-controlled booster dose portion of Study C4591001. The overall safety profile for the booster dose was similar to that seen after 2 doses.

In Study C4591031, a placebo-controlled booster study, 5,081 participants 16 years of age and older were recruited from Study C4591001 to receive a booster dose of COMIRNATY (tozinameran) at least 6 months after the second dose. The overall safety profile for the booster dose was similar to that seen after 2 doses.

In a subset of C4591007 Phase 2/3 participants, 401 participants 5 to <12 years of age received a booster dose of COMIRNATY (tozinameran) after completing the primary series. 399 of 401 participants in the safety population received the booster dose at 7 - < 9 months after Dose 2 (n = 51 [12.7%] at 7 - < 8 months and n = 348 [86.8%] at 8 - < 9 months). The overall safety profile for the booster dose was similar to that seen after the primary series.

Participants 16 years of age and older – after 2 doses

In Study C4591001, a total of 22,026 participants 16 years of age or older received at least 1 dose of COMIRNATY (tozinameran) 30 micrograms 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 COMIRNATY (tozinameran) and placebo groups, respectively). A total of 20,519 participants 16 years of age or older received 2 doses of COMIRNATY (tozinameran).

At the time of the analysis of Study C4591001 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 (tozinameran) 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 (tozinameran) and 7,407 placebo] participants 16 to 55 years of age and a total of 10,540 [5,327 COMIRNATY (tozinameran) and 5,213 placebo] participants 56 years 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 subjects receiving COMIRNATY (tozinameran), that were seropositive for SARS-CoV-2 at baseline, was similar to that seen in the general population.

Study C4591001 also included 200 participants with confirmed stable human immunodeficiency virus (HIV) infection. The safety profile of the participants receiving COMIRNATY (tozinameran) (n=100) in the individuals with stable HIV infection 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 C4591001, 2,260 adolescents [1,131 COMIRNATY (tozinameran) 30 micrograms; 1,129 placebo] were 12 to 15 years of age. Of these, 1,559 adolescents [786 COMIRNATY (tozinameran) and 773 placebo] have been followed for ≥ 4 months after the second dose of COMIRNATY (tozinameran). The safety evaluation in Study C4591001 is ongoing.

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%).

Children 5 to <12 years of age – after 2 doses

In an analysis of Study C4591007 Phase 2/3, 2,268 children [1,518 COMIRNATY (tozinameran) 10 micrograms; 750 placebo] were 5 to <12 years of age. Of these, 2,158 (95.1%) [1,444 COMIRNATY (tozinameran) 10 micrograms and 714 placebo] children have been followed for at least 2 months after the second dose. The safety evaluation in Study C4591007 is ongoing.

The most frequent adverse reactions in children 5 to <12 years of age that received 2 doses included injection site pain (>80%), fatigue (>50%), headache (>30%), injection site redness and swelling (>20%), myalgia and chills (>10%).

Children 2 to <5 years of age – after 3 doses

In an analysis of Study C4591007 (Phase 2/3), 2,750 children [1,835 COMIRNATY (tozinameran) 3 micrograms and 915 placebo] were 2 to <5 years age. Based on data in the blinded placebo-controlled follow-up period up to the cutoff date of 29 April 2022, 886 children 2 to <5 years of age who received a 3-dose primary course [606 COMIRNATY (tozinameran) 3 micrograms 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 <5 years of age that received any primary course dose included pain at injection site and fatigue (>40%), injection site redness and fever (>10%).

Infants 6 months to <2 years of age – after 3 doses

In an analysis of Study C4591007 (Phase 2/3), 1,776 infants [1,178 COMIRNATY (tozinameran) 3 micrograms and 598 placebo] were 6 months to <2 years of age. Based on data in the blinded placebo-controlled follow-up period up to the cutoff date of 29 April 2022, 570 infants 6 months to <2 years of age who received a 3-dose primary course [386 COMIRNATY 3 micrograms 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 months to <2 years of age that received any primary course dose included irritability (>60%), decrease appetite (>30%), tenderness at the injection site (>20%), injection site redness and fever (>10%).

Participants 16 years of age and older – after booster dose

A subset from Study C4591001 Phase 2/3 participants of 306 adults 18 to 55 years of age who completed the original COMIRNATY (tozinameran) 2-dose course, received a booster dose of COMIRNATY (tozinameran) approximately 6 months (range of 4.8 to 8.0 months) after receiving Dose 2. Of these, 301 participants have been followed for ≥4 months after the booster dose of COMIRNATY (tozinameran).

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 C4591031, a placebo-controlled booster study, participants 16 years of age and older recruited from Study C4591001 received a booster dose of COMIRNATY (tozinameran) (5,081 participants), or placebo (5,044 participants) at least 6 months after the second dose of COMIRNATY (tozinameran).

Overall, participants who received a booster dose, had a median follow-up time of 2.8 months (range 0.3 to 7.5 months) after the booster dose in the blinded placebo-controlled follow-up period to the cut-off date (8 February 2022). Of these, 1281 participants (895 COMIRNATY and 386 placebo) have been followed for ≥ 4 months after the booster dose of COMIRNATY (tozinameran).

Participants 18 years of age and older – after subsequent booster doses

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 (tozinameran 30 micrograms) 90 to 180 days after receiving Dose 3. Participants who received a booster (fourth dose) of COMIRNATY (tozinameran 30 micrograms) had a median follow-up time of 1.4 months. 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 C4591031 (Phase 3), 305 adults greater than 55 years of age who had completed 3 doses of COMIRNATY (tozinameran), received a booster (fourth dose) of COMIRNATY (tozinameran 30 micrograms) 5.3 to 13.1 months after receiving Dose 3. Participants who received a booster (fourth dose) of COMIRNATY (tozinameran 30 micrograms) had a median follow-up time of at least 1.7 months up to a data cutoff date of 16 May 2022. The most frequent adverse reactions in participants greater than 55 years of age were injection site pain (60%), fatigue (>40%), headache (>20%), myalgia and chills (>10%).

Children 5 to <12 years of age – after booster dose

In a subset from C4591007, a total of 401 children 5 to <12 years of age received a booster dose of COMIRNATY (tozinameran) 10 micrograms after completing the primary series. 399 of 401 participants in the safety population received the booster dose at 7 - < 9 months after Dose 2 (n = 51 [12.7%] at 7 - < 8 months and n = 348 [86.8%] at 8 - < 9 months). The analysis of the C4591007 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 most frequent adverse reactions in participants 5 to <12 years of age were injection site pain (>70%), fatigue (>40%), headache (>30%), myalgia, chills, injection site redness, and swelling (>10%). A higher frequency of lymphadenopathy was observed in C4591007 in participants receiving a booster dose compared to participants receiving 2 doses (2.5% vs. 0.9%).

Tabulated list of adverse reactions from clinical studies

Adverse reactions observed during clinical studies are listed below according to the following frequency categories:

Very common (≥1/10),
Common (≥1/100 to <1/10),
Uncommon (≥1/1,000 to <1/100),
Rare (≥1/10,000 to <1/1,000),
Very rare (<1/10,000),
Not known (cannot be estimated from the available data).

Table 1: Adverse reactions from COMIRNATY Original/Omicron BA.4-5 clinical trial (C4591044 Cohort 2 and Cohort 3 combined): Individuals 18 to 55 years and >55 years of age (Cohort 2 12 October 2022 Data Cut-off Date and Cohort 3 31 October 2022 Data Cut-off Date)

System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Not known (cannot be estimated from the available data)
Blood and lymphatic system disorders			Lymphadenopathy (18-55)	Lymphadenopathy (>55)	
Immune system disorders				Urticaria[b] (18-55) Pruritus[b] (>55)	
Nervous system disorders	Headache				
Gastrointestinal disorders		Vomitting[a] Diarrhoea[a] (>55)	Diarrhoea[a] (18-55)		
Musculoskeletal and connective tissue disorders	Arthralgia; Myalgia			Pain in extremity (arm)[b] (>55)	
General disorders and administration site conditions	Injection site pain; Fatigue; Chills;	Pyrexia; Injection site swelling; Injection site redness			

a. These adverse reactions were identified in the post-authorisation period.
b. The following events are categorised as hypersensitivity reactions: urticaria, pruritus, rash, and angioedema.

Table 2: Adverse reactions from COMIRNATY Original/Omicron BA.4-5 clinical trial (C4591044 Cohort 2): Individuals 12 to 17 years of age (12 October 2022 Data Cut-off Date)

System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Not known (cannot be estimated from the available data)
Blood and lymphatic system disorders					
Nervous system disorders	Headache				
Gastrointestinal disorders		Diarrhoea [a]; Vomiting [a]			
Musculoskeletal and connective tissue disorders	Arthralgia; Myalgia				
General disorders and administration site conditions	Injection site pain; Fatigue; Chills;	Pyrexia; Injection site swelling; Injection site redness			

[a] These adverse reactions were identified in the post-authorisation period.

Table 3: Adverse reactions from COMIRNATY Original/Omicron BA.4-5 clinical trial (C4591048 SSD): Individuals 5 to <12 years of age (25 November 2022 Data Cut-off Date)

System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Not known (cannot be estimated from the available data)
Blood and lymphatic system disorders			Lymphadenopathy		
Nervous system disorders	Headache				
Gastrointestinal disorders		Diarrhoea[a]; Vomiting[a]			
Musculoskeletal and connective tissue disorders	Myalgia	Arthralgia			
General disorders and administration site conditions	Injection site pain; Fatigue	Pyrexia; Chills; Injection site swelling; Injection site redness			

[a]. These adverse reactions were identified in the post-authorisation period

Table 4: Adverse reactions from COMIRNATY Original/Omicron BA.4-5 clinical trial (C4591048 SSB): Individuals 2 Years to <5 Years of Age (30 November 2022 Data Cut-off Date)

System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Not known (cannot be estimated from the available data)
Nervous system disorders		Headache[a]			
Gastrointestinal disorders		Vomiting[a]; Diarrhoea[a]			
Musculoskeletal and connective tissue disorders		Myalgia[a]; Arthralgia[a]			
General disorders and administration site conditions	Injection site pain;[a] Fatigue[a]	Pyrexia[a]; Injection site redness[a]; Chills[a]; Injection site swelling[a]			

a. These adverse reactions were identified in the post-authorisation period.

Table 5: Adverse reactions from COMIRNATY Original/Omicron BA.4-5 clinical trial (C4591048 SSB): Individuals 6 Months to <2 Years of Age (30 November 2022 Data Cut-off Date)

System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Not known (cannot be estimated from the available data)
Metabolism and nutrition disorders	Decreased appetite[a]				
Psychiatric disorders	Irritability[a]				
Gastrointestinal disorders		Diarrhoea; Vomiting			
General disorders and administration site conditions		Pyrexia[a]; Injection site tenderness[a]; Fatigue[a]; Injection site swelling[a]; Injection site redness[a]			

a. These adverse reactions were identified in the post-authorisation period. At the time of the data cut-off date, the following reactions were not reported in participants 6 months to <2 years of age in Study C4591048: pruritus, angioedema, dizziness, lethargy, myocarditis, pericarditis, hyperhidrosis, night sweats, and malaise but are still considered ADRs for this age group.

Table 6: Adverse reactions from COMIRNATY (tozinameran) clinical trial (C4591001): Individuals 12 years of age and older

System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Not known (cannot be estimated from the available data)
Blood and lymphatic system disorders			Lymphadenopathy[a]		
Psychiatric disorders			Insomnia		
Metabolism and nutrition disorders			Decreased appetite		
Nervous system disorders	Headache		Lethargy	Acute peripheral facial paralysis[b]	
Gastrointestinal disorders		Nausea			
Skin and subcutaneous disorders			Hyperhidrosis Night sweats		
Musculoskeletal and connective tissue disorders	Arthralgia; Myalgia				
General disorders and administration site conditions	Injection site pain; Fatigue; Chills; Pyrexia[c]; Injection site swelling	Injection site redness	Asthenia Malaise		Facial swelling[d]

a A higher frequency of lymphadenopathy (5.2% vs 0.4%) was observed in participants receiving a booster dose compared to participants receiving 2 doses.
b 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 COMIRNATY (tozinameran) 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.
c A higher frequency of pyrexia was observed after the second dose.
d Facial swelling in vaccine recipients with a history of injection of dermatological fillers

The safety profile in 545 subjects receiving COMIRNATY (tozinameran), that were seropositive for SARS-CoV-2 at baseline, was similar to that seen in the general population.

Table 7. Adverse Reactions from COMIRNATY (tozinameran) clinical trial (C4591007): Individuals 5 to <12 Years of Age (06 September 2021 Data Cut-off Date)

System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Not known (cannot be estimated from the available data)
Blood and lymphatic system disorders			Lymphadenopathy[a]		
Immune system disorders			Urticaria[b,c]; Pruritus[b,c]; Rash[b,c]		Anaphylaxis[b]
Metabolism and nutrition disorders			Decreased appetite		
Nervous system disorders	Headache				
Gastrointestinal disorders		Diarrhoea;[b] Vomiting[b]	Nausea		
Musculoskeletal and connective tissue disorders	Myalgia	Arthralgia	Pain in extremity (arm)[b]		
General disorders and administration site conditions	Injection site pain; Fatigue; Chills; Injection site swelling; Injection site redness	Pyrexia	Malaise		

[a] A higher frequency of lymphadenopathy was observed in C4591007 (2.5% vs. 0.9%) in participants receiving a booster dose compared to participants receiving 2 doses.
[b] These adverse reactions were identified in the post-authorisation period. The following events were not reported in participants 5 to <12 Years of Age in Study C4591007 but were reported in individuals ≥16 years of age in Study C4591001: angioedema, lethargy, asthenia, hyperhidrosis, and night sweats.
[c] The following events are categorised as hypersensitivity reactions: urticaria, pruritus, and rash
a. These adverse reactions were identified in the post-authorisation period. At the time of the data-lock, the following reactions were not reported in participants 2 to <5 Years of Age in Study C4591007: pruritus, angioedema, lethargy, myocarditis, pericarditis, hyperhidrosis, night sweats, and malaise.
b. The following events are categorised as hypersensitivity reactions: rash and urticaria

Table 8. Adverse Reactions from COMIRNATY (tozinameran) clinical trial: Individuals 2 to <5 Years of Age (29 April 2022 Data Cut-off Date)

System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Very Rare <1/10,000	Not known (cannot be estimated from the available data)
Blood and lymphatic system disorders			Lymphadenopathy			
Immune system disorders			Rash[a,b]; Urticaria[a,b]			Anaphylaxis[a]
Metabolism and nutrition disorders			Decreased appetite			
Nervous system disorders		Headache				
Cardiac disorders					Myocarditis[a] Pericarditis[a]	
Gastrointestinal disorders	Diarrhoea[a]	Vomiting[a]	Nausea			
Musculoskeletal and connective tissue disorders		Myalgia Arthralgia	Pain in extremity (arm)[a]			
General disorders and administration site conditions	Injection site pain; Fatigue; Injection site redness; Pyrexia	Injection site swelling; Chills	Asthenia			

Table 9. Adverse Reactions from COMIRNATY (tozinameran) clinical trial: Individuals 6 Months to <2 Years of Age (29 April 2022 Data Cut-off Date)

System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Very Rare <1/10,000	Not known (cannot be estimated from the available data)
Blood and lymphatic system disorders			Lymphadenopathy			
Immune system disorders		Rash[a,b]	Urticaria[a,b];			Anaphylaxis[a]
Metabolism and nutrition disorders	Decreased appetite					
Cardiac disorders					Myocarditis[a] Pericarditis[a]	
Psychiatric disorders	Irritability					
Nervous system disorders			Headache Lethargy			
Gastrointestinal disorders		Vomiting[a,]; Diarrhoea[a,]				
General disorders and administration site conditions	Injection site tenderness; Injection site redness; Pyrexia	Injection site swelling	Fatigue; Chills			

a. These adverse reactions were identified in the post-authorisation period. At the time of data-lock, the following events were not reported in participants 6 months to <2 Years of Age in Study C4591007: pruritus, angioedema, nausea, hyperhidrosis, night sweats,

myalgia, arthralgia, pain in extremity, malaise, and asthenia.

b. The following events are categorised as hypersensitivity reactions: rash and urticaria

Post-marketing experience

Although the events listed in Table 10 were not observed in the clinical trials, they are considered adverse drug reactions for COMIRNATY as they were reported in the post-marketing experience. As these reactions were derived from spontaneous reports, the frequencies could not be determined and are thus considered as not known.

Table 10: Adverse reactions from COMIRNATY post marketing experience

System Organ Class	Adverse Drug Reaction
Immune system disorders	Anaphylaxis Hypersensitivity reactions (e.g. rash, pruritis, urticaria, angioedema, erythema multiforme)
Cardiac disorders	Myocarditis Pericarditis
Gastrointestinal disorders	Diarrhoea Vomiting
Musculoskeletal and connective tissue disorders	Pain in extremity (arm)[a]
General disorders and administration site conditions	Extensive swelling of vaccinated limb
Nervous system disorders	Paraesthesia Hypoaesthesia Dizziness Headache (including migraine)
Reproductive system and breast disorders	Non-sexually acquired genital ulceration Heavy menstrual bleeding*

[a] A higher frequency of pain in extremity (1.1% vs. 0.8%) was observed in participants receiving a booster dose in Study C4591031 compared to participants receiving 2 doses.

* Most cases appear to be non-serious and temporary in nature

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

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 (tozinameran). The COMIRNATY 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.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

The nucleoside-modified messenger RNA in the vaccine 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 spike (S) antigen. The mRNA codes for membrane-anchored, full-length S with two point mutations within the central helix. Mutation of these two amino acids to proline locks S in an antigenically preferred prefusion conformation. The vaccine elicits both neutralising antibody and cellular immune responses to the antigen, which may contribute to protection against COVID-19.

Clinical trials

Immunogenicity

COMIRNATY Original/Omicron BA.4-5 (tozinameran/famtozinameran)

Relative vaccine immunogenicity in participants 12 years of age and older – after bivalent Omicron BA.4-5 (second booster dose)

In an analysis of a subset from Study C4591044, 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 (tozinameran) received COMIRNATY Original/Omicron BA.4-5 (15/15 micrograms) as a second booster. 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% neutralising antibody titres (NT50) against Omicron BA.4-5 and against reference strain among participants 56 years of age and older who received COMIRNATY Original/Omicron BA.4-5 as a second booster in Study C4591044 compared to a subset of participants from Study C4591031 who received a second booster of COMIRNATY (tozinameran) demonstrated superiority of COMIRNATY Original/Omicron BA.4-5 to COMIRNATY (tozinameran) 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 11 and Table 12).

Analyses of NT50 against Omicron BA.4-5 among participants 18 to 55 years of age compared to participants 56 years of age and older who received COMIRNATY Original/Omicron BA.4-5 as a booster dose in Study C4591044 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 11 and Table 12).

The study also assessed the level of NT50 of the anti-Omicron BA.4-5 and original SARS-COV-2 strains pre-vaccination and 1 month after vaccination in participants who received COMIRNATY Original/Omicron BA.4-5 as a second booster dose (Table 13).

Table 11: Geometric Mean Ratios – Study C4591044 – Participants With or Without Evidence of Infection - Evaluable Immunogenicity Population

SARS-CoV-2 neutralisation assay	Sampling time point[a]	COMIRNATY Original/Omicron BA.4-5 C4591044				COMIRNATY (tozinameran) Subset of C4591031		Age group comparison	Vaccine group comparison ≥ 56 years
		18 - 55 years of age		≥ 56 years of age		≥ 56 years of age		COMIRNATY Original/ Omicron BA.4-5 18 - 55 years / ≥56 years of age	COMIRNATY Original/ Omicron BA.4-5 /COMIRNATY
		n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])	GMR[d] (95% CI[d])	GMR[d] (95% CI[d])
Omicron BA.4-5 - NT50 (titre)[e]	1 month	297	4455.9 (3851.7, 5154.8)	284	4158.1 (3554.8, 4863.8)	282	938.9 (802.3, 1098.8)	0.98 (0.83, 1.16)[f]	2.91 (2.45, 3.44)[g]
Reference strain - NT50 (titre)[e]	1 month	-	-	286	16250.1 (14499.2, 18212.4)	289	10415.5 (9366.7, 11581.8)	-	1.38 (1.22, 1.56)[h]

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

a. Protocol-specified timing for blood sample collection.

b. n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.

c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.

d. GMRs and 2-sided 95% CIs were calculated by exponentiating the difference of LS means and corresponding CIs based on analysis of logarithmically transformed neutralising titres using a linear regression model with terms of baseline neutralising titre (log scale) and vaccine group or age group.

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).

f. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67.

g. Superiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 1.

h. 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.

Table 12: Difference in Percentages of Participants with Seroresponse of COMIRNATY Original/Omicron BA.4-5 from Study C4591044 and COMIRNATY (tozinameran) from Subset of Study C4591031 – Participants With or Without Evidence of Infection – Evaluable Immunogenicity Population

SARS-CoV-2 neutralisation assay	Sampling time point[a]	COMIRNATY Original/Omicron BA.4-5 C4591044				COMIRNATY (tozinameran) Subset of C4591031		Age group comparison	Vaccine group comparison ≥ 56 years
		18 - 55 years of age		≥ 56 years of age		≥ 56 years of age		COMIRNATY Original/Omicron BA.4-5 18 - 55 years / ≥ 56 years of age	COMIRNATY Original/Omicron BA.4-5 /COMIRNATY
		n[b]	N[c] (%) (95% CI[d])	n[b]	N[c] (%) (95% CI[d])	n[b]	N[c] (%) (95% CI[d])	Difference[e] (95% CI[f])	Difference[e] (95% CI[f])
Omicron BA.4-5 - NT50 (titre)[g]	1 month	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)[h]	26.77 (19.59, 33.95)[i]

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

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

a. Protocol-specified timing for blood sample collection.

b. N = Number of participants with valid and determinate assay results for the specified assay at both the prevaccination time point

and the given sampling time point. This value is the denominator for the percentage calculation.
c. n = Number of participants with seroresponse for the given assay at the given sampling time point.
d. Exact 2-sided CI, based on the Clopper and Pearson method.
e. Difference in proportions, expressed as a percentage.
f. 2-sided CI based on the Miettinen and Nurminen method stratified by baseline neutralising titre category (< median, ≥ median) for the difference in proportions. The median of baseline neutralising titres was calculated based on the pooled data in 2 comparator groups.
g. SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (Omicron B.1.1.529 subvariant BA.4/BA.5).
h. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is > -10%.
i. 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 13: Geometric Mean Titres by Baseline SARS-CoV-2 Status – Subsets of Study C4591044 – Prior to and 1 month after COMIRNATY Original/Omicron BA.4-5 as a Second Booster – Participants 12 years of age and older – Evaluable Immunogenicity Population

SARS-CoV-2 neutralisation assay	Baseline SARS-CoV-2 Status	Sampling time point[a]	COMIRNATY Original/Omicron BA.4-5					
			12 - 17 years of age		18 - 55 years of age		≥ 56 years of age	
			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)[f]	All	Pre-vaccination	104	1105.8 (835.1, 1464.3)	294	569.6 (471.4, 688.2)	284	458.2 (365.2, 574.8)
		1 month	105	8212.8 (6807.3, 9908.7)	297	4455.9 (3851.7, 5154.8)	284	4158.1 (3554.8, 4863.8)
	Positive[d]	Pre-vaccination	78	1791.1 (1379.6, 2325.3)	210	1181.4 (1005.3, 1388.3)	174	1291.7 (1027.5, 1623.8)
		1 month	79	9892.5 (8114.6, 12059.8)	213	6031.6 (5203.9, 6991.0)	176	6688.9 (5664.4, 7898.8)
	Negative[e]	Pre-vaccination	26	260.2 (157.1, 430.9)	84	91.9 (71.5, 118.1)	110	88.9 (69.8, 113.4)
		1 month	26	4666.1 (3096.1, 7032.2)	84	2067.7 (1530.2, 2793.9)	108	1916.2 (1489.5, 2465.1)
Reference strain - NT50 (titre)[f]	All	Pre-vaccination	105	6863.3 (5587.8, 8430.1)	296	4017.3 (3430.7, 4704.1)	284	3690.6 (3082.2, 4419.0)
		1 month	105	23641.3 (20473.1, 27299.8)	296	16323.3 (14686.5, 18142.6)	286	16250.1 (14499.2, 18212.4)
	Positive[d]	Pre-vaccination	79	8685.4 (7062.7, 10680.9)	213	7068.6 (6251.9, 7992.0)	174	8082.1 (6843.6, 9544.8)
		1 month	79	25991.8 (22377.5, 30189.8)	212	19076.6 (17056.5, 21336.0)	176	21273.3 (18604.2, 24325.3)
	Negative[e]	Pre-vaccination	26	3356.2 (2106.9, 5346.2)	83	942.3 (705.6, 1258.3)	110	1068.0 (835.9, 1364.6)
		1 month	26	17725.2 (12376.4, 25385.7)	84	11014.6 (8793.9, 13796.0)	110	10560.6 (8827.1, 12634.5)

Abbreviations: CI = confidence interval; GMT = geometric mean titre; LLOQ = lower limit of quantitation; NT50 = 50% neutralising titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
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. Positive N-binding antibody result at baseline, positive NAAT result at baseline, or medical history of COVID-19.
e. Negative N-binding antibody result at baseline, negative NAAT result at baseline, and no medical history of COVID-19.
f. SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).

Relative vaccine immunogenicity in participants 5 to <12 years of age– after bivalent Omicron BA.4-5 (second booster dose)

In an analysis of a subset from Study C4591048, 103 participants 5 to <12 years of age who had previously received a 2-dose primary series and a booster dose with COMIRNATY (tozinameran) received COMIRNATY Original/Omicron BA.4-5 (5/5 micrograms) as a second booster. Results include immunogenicity data from a comparator subset of participants 5 to < 12 years of age in Study C4591007 who received 3 doses of COMIRNATY (tozinameran).

The immune response 1 month after a booster dose, COMIRNATY Original/Omicron BA.4-5 elicited generally similar Omicron BA.4-5-specific neutralising titres compared with the titres in the comparator group who received 3 doses of COMIRNATY (tozinameran). 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 < 12 years of age are presented in Table 14.

Table 14: Study C4591048 SSD – Geometric Mean Titres, by Baseline (Dose 4 Study C4591048/Dose 3 Study C4591007) SARS-CoV-2 Status – Participants With or Without Evidence of Infection – 5 to < 12 Years of Age – Evaluable Immunogenicity Population

			Vaccine Group (as Assigned/Randomised)			
			C4591048 SSD COMIRNATY Original/Omicron BA.4-5 5/5 mcg Dose 4 and 1 Month After Dose 4		C4591007 COMIRNATY (tozinameran) 10 mcg Dose 3 and 1 Month After Dose 3	
SARS-CoV-2 neutralisation Assay	**Baseline SARS-CoV-2 Status**	**Sampling Time Point[a]**	**n[b]**	**GMT[c] (95% CI[c])**	**n[b]**	**GMT[c] (95% CI[c])**
Omicron BA.4-5 - NT50 (titre)[f]	Overall	Pre-vaccination	102	488.3 (361.9, 658.8)	112	248.3 (187.2, 329.5)
		1 Month	102	2189.9 (1742.8, 2751.7)	112	1393.6 (1175.8, 1651.7)
	Positive[d]	Pre-vaccination	58	1069.2 (782.4, 1461.1)	65	695.0 (538.4, 897.3)
		1 Month	58	3465.6 (2682.8, 4476.7)	65	1893.9 (1547.6, 2317.7)
	Negative[e]	Pre-vaccination	44	173.8 (117.3, 257.4)	47	59.8 (49.0, 73.1)
		1 Month	44	1195.8 (850.2, 1681.9)	47	905.8 (703.0, 1167.2)
Reference strain - NT50 (titre)[f]	Overall	Pre-vaccination	102	2904.0 (2372.6, 3554.5)	113	1323.1 (1055.7, 1658.2)
		1 Month	102	8245.9 (7108.9, 9564.9)	113	7235.1 (6331.5, 8267.8)
	Positive[d]	Pre-vaccination	58	4198.4 (3342.9, 5272.8)	66	2672.7 (2122.4, 3365.6)
		1 Month	58	9228.4 (7707.0, 11050)	66	7632.5 (6471.6, 9001.5)
	Negative[e]	Pre-vaccination	44	1786.4 (1305.0, 2445.5)	47	492.9 (390.9, 621.6)
		1 Month	44	7108.8 (5534.0, 9131.8)	47	6711.9 (5345.4, 8427.7)

Abbreviations: 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.

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 titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.

d. For Study 6: positive N-binding antibody result at the Dose 4 visit, positive NAAT result at the Dose 4 visit, or medical history of COVID-19. For Study 3: positive N-binding antibody result at the Dose 1, 1-month post–Dose 2 (if available), or Dose 3 visit, positive NAAT result at the Dose 1, Dose 2, Dose 3, or any unscheduled illness visit up to the Dose 3 visit, or medical history of COVID-19.

e. For Study 6: negative N-binding antibody result at the Dose 4 visit, negative NAAT result at the Dose 4 visit, and no medical history of COVID-19. For Study 3: negative N-binding antibody result at the Dose 1, 1-month post–Dose 2 (if available), and Dose 3 visits, negative NAAT result at the Dose 1, Dose 2, Dose 3, and any unscheduled illness visits up to the Dose 3 visit, and no medical history of COVID-19.

f. SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).

Immunogenicity in participants 6 months to <5 years of age – after bivalent Omicron BA.4-5 (booster dose)

In an interim analysis of C4591048, 310 participants (92 participants 6 months to <2 years of age and 218 participants 2 years to <5 years of age) received COMIRNATY Original/Omicron BA.4-5 (1.5/1.5 micrograms) as a booster dose after receiving 3 prior doses of COMIRNATY (tozinameran), data cut-off date 3 March 2023. The average number of days between the Dose 3 to Dose 4 was approximately 174 days (range 59 – 241 days). Results include immunogenicity data from a comparator subset of participants 6 months to <5 years of age in C4591007 who received 3 doses of COMIRNATY (tozinameran).

At 1 month after a booster dose, COMIRNATY Original/Omicron BA.4-5 elicited higher Omicron BA.4-5-specific neutralising titres compared with the titres in the comparator group who received 3 doses of COMIRNATY (tozinameran). 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 6 months to <5 years of age are presented in Table 15.

Table 15. Study C4591048 SSB Group 2 - Geometric Mean Titres & Geometric Mean Fold Rises, by Baseline (Dose 4) SARS-CoV-2 Status – Participants With or Without Evidence of Infection – 6 Months to <5 Years of Age – Evaluable Immunogenicity Population

SARS-CoV-2 Neutralisation Assay	Age Group	Baseline SARS-CoV-2 Status	Sampling Time Point[a]	Vaccine Group (as Assigned/Randomised)			
				C4591048 SSB COMIRNATY Original/Omicron BA.4-5 1.5/1.5 mcg Dose 4 and 1 Month After Dose 4			
				n[b]	GMT[c] (95% CI[c])	n[b]	GMFR[c] (95% CI[c])
Omicron BA.4/BA.5 - NT50 (titre)[f]	6 months to <5 years	Overall	Pre-vaccination	266	241.7 (197.3, 296.1)	266	9.3 (8.0, 10.7)
			1 month	274	2237.2 (1884.8, 2655.5)		
		Positive[d]	Pre-vaccination	110	1107.7 (893.5, 1373.3)	110	6.0 (4.9, 7.4)
			1 month	112	6624.5 (5587.5, 7854.0)		

SARS-CoV-2 Neutralisation Assay	Age Group	Baseline SARS-CoV-2 Status	Sampling Time Point[a]	Vaccine Group (as Assigned/Randomised) C4591048 SSB COMIRNATY Original/Omicron BA.4-5 1.5/1.5 mcg Dose 4 and 1 Month After Dose 4 n[b]	GMT[c] (95% CI[c])	n[b]	GMFR[c] (95% CI[c])
		Negative[e]	Pre-vaccination	153	81.4 (69.2, 95.8)	153	12.5 (10.4, 15.1)
			1 month	155	1040.9 (853.4, 1269.5)		
	6 to 23 months	Overall	Pre-vaccination	74	293.9 (195.4, 441.9)	74	6.7 (5.1, 8.8)
			1 month	78	1905.1 (1328.9, 2731.2)		
		Positive[d]	Pre-vaccination	36	1129.2 (741.6, 1719.2)	36	5.3 (3.6, 7.6)
			1 month	36	5948.3 (4272.9, 8280.5)		
		Negative[e]	Pre-vaccination	36	75.3 (55.4, 102.5)	36	8.4 (5.6, 12.6)
			1 month	38	697.0 (446.5, 1087.9)		
	2 to <5 years	Overall	Pre-vaccination	192	224.1 (177.2, 283.5)	192	10.5 (8.9, 12.5)
			1 month	196	2384.9 (1965.4, 2893.9)		
		Positive[d]	Pre-vaccination	74	1097.4 (852.3, 1413.1)	74	6.4 (5.0, 8.3)
			1 month	76	6971.2 (5705.2, 8518.2)		
		Negative[e]	Pre-vaccination	117	83.4 (68.8, 101.1)	117	14.2 (11.6, 17.4)
			1 month	117	1185.7 (953.0, 1475.2)		
Reference strain - NT50 (titre)[f]	6 months to <5 years	Overall	Pre-vaccination	266	1721.9 (1491.0, 1988.4)	266	4.3 (3.8, 4.8)
			1 month	274	7409.3 (6649.4, 8256.1)		
		Positive[d]	Pre-vaccination	110	3549.5 (2922.2, 4311.5)	110	2.8 (2.5, 3.2)
			1 month	112	10080.7 (8720.9, 11652.5)		
		Negative[e]	Pre-vaccination	153	1046.7 (888.7, 1232.7)	153	5.6 (4.8, 6.6)
			1 month	155	5910.6 (5082.7, 6873.4)		
	6 to 23 months	Overall	Pre-vaccination	74	1688.3 (1271.6, 2241.6)	74	3.7 (2.9, 4.7)
			1 month	78	6312.0 (5143.6, 7746.0)		
		Positive[d]	Pre-vaccination	36	3050.0 (2123.6, 4380.5)	36	2.6 (2.0, 3.4)
			1 month	36	7979.2 (5949.9, 10700.7)		
		Negative[e]	Pre-vaccination	36	981.3 (676.5, 1423.2)	36	4.9 (3.4, 7.1)
			1 month	38	5064.3 (3722.6, 6889.5)		

SARS-CoV-2 Neutralisation Assay	Age Group	Baseline SARS-CoV-2 Status	Sampling Time Point[a]	Vaccine Group (as Assigned/Randomised) C4591048 SSB COMIRNATY Original/Omicron BA.4-5 1.5/1.5 mcg Dose 4 and 1 Month After Dose 4 n[b]	GMT[c] (95% CI[c])	n[b]	GMFR[c] (95% CI[c])
	2 to <5 years	Overall	Pre-vaccination	192	1734.9 (1466.0, 2053.3)	192	4.5 (3.9, 5.2)
			1 month	196	7897.3 (6952.0, 8971.2)		
		Positive[d]	Pre-vaccination	74	3821.3 (3025.6, 4826.3)	74	2.9 (2.5, 3.5)
			1 month	76	11261.1 (9586.2, 13228.7)		
		Negative[e]	Pre-vaccination	117	1067.7 (888.4, 1283.2)	117	5.8 (4.9, 6.9)
			1 month	117	6214.9 (5218.5, 7401.6)		

Abbreviations: GMT = geometric mean titre; GMFR = geometric mean fold rise; 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: Substudy B Group 2 includes participants ≥6 months to <5 years of age who received 3 doses of BNT162b2 3 µg 60 to 240 days prior to enrolment.

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/GMFRs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres/fold rises and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.

d. For C4591048 Substudy B Group 2: positive N-binding antibody result at Dose 4 visit, positive NAAT result at Dose 4 visit, or medical history of COVID-19.

e. For C4591048 Substudy B Group 2: negative N-binding antibody result at Dose 4 visit, negative NAAT result at Dose 4 visit, and no medical history of COVID-19.

f. SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).

Overall, 22 cases of COVID-19 were reported in participants ≥6 months to <5 years (9 cases in ≥6 months to <2 years, 13 cases in ≥2 to <5 years) who received a fourth dose of bivalent BNT162b2 (Original/Omi BA.4/BA.5). Lineage for the cases was determined as follows: Among the determinate and quantifiable sequence, lineage for the cases w identified as XBB.1.5 (Omicron) (n=4), BQ.1 (Omicron) (n= 2), BA.5.1.3 (Omicron) (n=1), BL.1 (Omicron) (n= 1), BQ.1.1 (Omicron) (n=1), BQ.1.1.18 (Omicron) (n=1), BQ.1.1.35 (Omicron) (n=1), BQ.1.25 (Omicron) (n=1), CQ.1.1 (Omicron) (n=1), FD.2 (Omicron) (n=1), XBB.1.5.14 (Omicron) (n=1), XBB.1.5.34 (Omicron) (n=1), and unknown due to insufficient quantity (n=5) or not sequenced (n=1).

Immunogenicity in participants 6 months to <5 years of age – bivalent Omicron BA.4-5 3-dose primary course

C4591048 Substudy A (SSA), a phase I, randomised, single-blinded, dose-finding study included evaluation of 1-month post-dose 3 safety and immunogenicity following 3 doses with COMIRNATY Original/Omicron BA.4-5 (1.5/1.5 micrograms) administered on a 0-, 3-, and 11-week schedule in participants 6 months to <5 years of age.

Descriptive immunogenicity analyses were performed to characterise Omicron BA.4/BA.5 and reference strain neutralisation responses following 3 doses with COMIRNATY Original/Omicron BA.4-5.

The vaccine immunogenicity results after a 3-dose series in participants 6 months to <5 years of age are presented in Table 16.

Table 16. Study C4591048 SSA - Geometric Mean Titres & Geometric Mean Fold Rises at 1 month after vaccination course (3-doses), by Baseline SARS-CoV-2 Status – Participants With or Without Evidence of Infection – 6 Months to <5 Years of Age – Evaluable Immunogenicity Population

SARS-CoV-2 Neutralisation Assay	Age Group	Baseline SARS-CoV-2 Status	Sampling Time Point[a]	Vaccine Group (as Randomised) C4591048 SSA COMIRNATY Original/Omicron BA.4-5 1.5/1.5 mcg 3-doses and 1 Month After Dose 3			
				n[b]	GMT[c] (95% CI[c])	n[b]	GMFR[c] (95% CI[c])
Omicron BA.4/BA.5 - NT50 (titre)	6 months to <5 years	Overall	Pre-vaccination	35	492.6 (247.2, 981.4)	25	15.5 (8.1, 29.5)
			1 month	29	10452.6 (7091.3, 15407.2)		
		Positive[d]	Pre-vaccination	28	950.6 (495.1, 1825.3)	21	10.0 (5.7, 17.3)
			1 month	21	12700.1 (7861.5, 20516.7)		
		Negative[e]	Pre-vaccination	7	35.5 (35.5, 35.5)	4	158.7 (31.2, 808.4)
			1 month	5	6659.9 (2017.3, 21986.4)		
Reference strain - NT50 (titre)	6 months to <5 years	Overall	Pre-vaccination	35	234.4 (147.3, 373.1)	25	22.7 (12.8, 40.3)
			1 month	29	6674.9 (4222.2, 10552.2)		
		Positive[d]	Pre-vaccination	28	322.3 (195.8, 530.5)	21	18.7 (10.2, 34.3)
			1 month	21	8370.1 (4725.8, 14824.8)		
		Negative[e]	Pre-vaccination	7	65.6 (32.7, 131.8)	4	64.1 (8.1, 507.3)
			1 month	5	4860.4 (2073.5, 11393.2)		

Abbreviations: GMT = geometric mean titre; GMFR = geometric mean fold rise; 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.

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/GMFRs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres/fold rises and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ..

d. Positive N-binding antibody result at Dose 1, positive NAAT result at Dose 1, or medical history of COVID-19.

e. Negative N-binding antibody result at Dose 1, negative NAAT result at Dose 1, and no medical history of COVID-19.

For C4591048 SSA: Evaluable immunogenicity (3-Dose) population.

COMIRNATY (tozinameran)

Study C4591001 is a multicentre, multinational, Phase 1/2/3 randomised, placebo-controlled, observer-blind dose-finding, vaccine candidate selection and efficacy study in participants 12 years of age and older. Randomisation was stratified by age: 12 to 15 years of age, 16 to 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥56-year stratum. The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19. Participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalisation for worsening disease during the 6 weeks before enrolment, were included as were participants with known stable infection with 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 C4591001, based on data accrued through 14 November 2020, approximately 44,000 participants were randomised equally and were to receive 2 doses of COMIRNATY (tozinameran) 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 COMIRNATY (tozinameran). 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 through to conclusion of the study in order to receive either placebo or COMIRNATY (tozinameran).

The population for the analysis of the primary efficacy endpoint included, 36,621 participants 12 years of age and older (18,242 in the COMIRNATY (tozinameran) 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 COMIRNATY (tozinameran) group and 68 in the placebo group) and 1616 participants 75 years of age and older (804 in the COMIRNATY (tozinameran) 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 COMIRNATY (tozinameran) group and in total 2,222 person-years for the placebo group.

There were no meaningful clinical differences in overall vaccine efficacy in participants who were at risk of severe COVID-19 including those with 1 or more comorbidities that increase the risk of severe COVID-19 (e.g. asthma, body mass index (BMI) ≥30 kg/m^2, chronic pulmonary disease, diabetes mellitus, hypertension).

COMIRNATY (tozinameran) efficacy information is presented in Table 17.

Table 17: 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	**COMIRNATY (tozinameran)** **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)[f]
All participants[e]	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 (3848)	19 0.511 (3880)	94.7 (66.7, 99.9)
65 to 74 years	1 0.406 (3074)	14 0.406 (3095)	92.9 (53.1, 99.8)
75 years and older	0 0.102 (774)	5 0.106 (785)	100.0 (-13.1, 100.0)

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

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

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

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

c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

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

e. No confirmed cases were identified in adolescents 12 to 15 years of age.

f. Two-sided confidence interval (CI) for vaccine efficacy (VE) is derived based on the Clopper and Pearson method adjusted to the surveillance time. CI not adjusted for multiplicity.

In the second primary analysis, efficacy of COMIRNATY (tozinameran) in preventing first COVID-19 occurrence from 7 days after Dose 2 compared to placebo was 94.6% (95% credible interval of 89.9% to 97.3%) 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 through 13 March 2021, representing up to 6 months of follow-up after Dose 2 for participants in the efficacy population.

The updated vaccine efficacy information is presented in Table 18.

Table 18: 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 during the placebo-controlled follow-up period

First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection*			
Subgroup	**COMIRNATY (tozinameran) 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 (4192)	124 1.202 (4226)	94.5 (88.3, 97.8)
65 to 74 years	6 0.994 (3350)	98 0.966 (3379)	94.1 (86.6, 97.9)
75 years and older	1 0.239 (842)	26 0.237 (847)	96.2 (76.9, 99.9)

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

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

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

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

c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

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

e. Two-sided 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 COMIRNATY (tozinameran) group (both without and with or without evidence of prior SARS-CoV-2 infection); 16 and 18 in the placebo group (without and with or without evidence of prior SARS-CoV-2 infection, respectively).

Efficacy against severe COVID-19 in participants 12 years of age and older – after 2 doses

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 19) 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 COMIRNATY (tozinameran) and placebo groups.

Table 19. Vaccine Efficacy – First Severe COVID-19 Occurrence in Participants With or Without* Prior SARS-CoV-2 Infection Based on Food and Drug Administration (FDA)† Definition After Dose 1 or From 7 Days After Dose 2 in the Placebo-Controlled Follow-up

	COMIRNATY (tozinameran) 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).

* 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.

† Severe illness from COVID-19 as defined by FDA is confirmed COVID-19 and presence of at least 1 of the following:

- Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥30 breaths per minute, heart rate ≥125 beats per minute, saturation of oxygen ≤93% on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen <300 mm Hg);
- Respiratory failure [defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
- Evidence of shock (systolic blood pressure <90 mm Hg, diastolic blood pressure <60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an Intensive Care Unit;
- Death.

a. n1 = Number of participants meeting the endpoint definition.
b. n2 = Number of participants at risk for the endpoint.
c. Two-side confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
d. Efficacy assessed based on the Dose 1 all available efficacy (modified intention-to-treat) population that included all randomised participants who received at least 1 dose of study intervention.
e. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.
f. Efficacy assessed based on the evaluable efficacy (7 Days) population that included all eligible randomised participants who receive all dose(s) of study intervention as randomised within the predefined window, have no other important protocol deviations as determined by the clinician
g. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

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

An analysis of Study C4591001 has been performed in adolescents 12 to 15 years of age up to a data cut-off date of 13 March 2021.

In an analysis of Study C4591001 in adolescents 12 to 15 years of age without evidence of prior infection, there were no cases in 1005 participants who received the vaccine and 16 cases out of 978 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 75.3, 100.0). In participants with or without evidence of prior infection there were 0 cases in the 1119 who received vaccine and 18 cases in 1110 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 78.1, 100.0). No cases of severe disease occurred in adolescents.

In Study C4591001, an analysis of SARS-CoV-2 neutralising titres in a randomly selected subset of participants was performed to demonstrate non-inferior immune responses (within 1.5-fold) comparing adolescents 12 to 15 years of age to participants 16 to 25 years of age who had no serological or virological evidence of past SARS-CoV-2 infection. The immune response to COMIRNATY (tozinameran) in adolescents 12 to 15 years of age (n = 190) was non-inferior to the immune response in participants 16 to 25 years of age (n = 170), based on results for SARS-CoV-2 neutralising titres at 1 month after Dose 2. The geometric mean titres (GMT) ratio of the adolescents 12 to 15 years of age group to the participants 16 to 25 years of age group was 1.76, with a 2-sided 95% CI of 1.47 to 2.10, meeting the 1.5-fold non-inferiority criterion (the lower bound of the 2-sided 95% CI for the geometric mean ratio [GMR] > 0.67).

An updated efficacy analysis of Study C4591001 has been performed in approximately 2,260 adolescents 12 to 15 years of age evaluating confirmed COVID-19 cases accrued up to a data

cut-off date of 2 September 2021, representing up to 6 months of follow-up after Dose 2 for participants in the efficacy population. The dominant SARS-CoV-2 variant at the time of the efficacy study was B.1.1.7 (Alpha).

The updated vaccine efficacy information in adolescents 12 to 15 years of age is presented in Table 20.

Table 20: Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2: Without Evidence of Infection and With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-up Period, Adolescents 12 To 15 Years of Age Evaluable Efficacy (7 Days) Population

First COVID-19 occurrence from 7 days after Dose 2 in adolescents 12 to 15 years of age without evidence of prior SARS-CoV-2 infection*			
	COMIRNATY (tozinameran) N[a]=1057 Cases n1[b] Surveillance Time[c] (n2[d])	**Placebo N[a]=1030 Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI[e])**
Adolescents 12 to 15 years of age	0 0.343 (1043)	28 0.322 (1019)	100.0 (86.8, 100.0)
First COVID-19 occurrence from 7 days after Dose 2 in adolescents 12 to 15 years of age with or without evidence of prior SARS-CoV-2 infection			
	COMIRNATY (tozinameran) N[a]=1119 Cases n1[b] Surveillance Time[c] (n2[d])	**Placebo N[a]=1109 Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI[e])**
Adolescents 12 to 15 years of age	0 0.362 (1098)	30 0.345 (1088)	100.0 (87.5, 100.0)

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

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

a. N = Number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Two-sided confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.

Efficacy in children 5 to <12 years of age – after 2 doses

A descriptive interim efficacy analysis of Study C4591007 has been performed in 1,968 children 5 to 11 years of age without evidence of infection prior to 7 days after Dose 2. This analysis evaluated confirmed symptomatic COVID-19 cases accrued up to a data cut-off date of 8 October 2021.

The descriptive vaccine efficacy results in children 5 to 11 years of age without evidence of prior SARS-CoV-2 infection are presented in Table 21. None of the cases accrued met criteria

for severe COVID-19 or multisystem inflammatory syndrome in children (MIS-C). 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 21: 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*			
	COMIRNATY± (tozinameran) 10 microgram/dose Na=1305 Cases n1b Surveillance Timec (n2d)	**Placebo Na=663 Cases n1b Surveillance Timec (n2d)**	**Vaccine Efficacy % (95% CI)**
Children 5 to 11 years of age	3 0.322 (1273)	16 0.159 (637)	90.7 (67.7, 98.3)

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

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

± Pfizer-BioNTech COVID-19 Vaccine (10 micrograms modRNA).

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

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

c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

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

Immunogenicity in children 5 to <12 years of age – after 2 doses

Study C4591007 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 <12 years of age.

In C4591007, 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 <12 years of age in the Phase 2/3 part of Study C4591007 to participants 16 to 25 years of age in the Phase 2/3 part of Study C4591001 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 ratio of the SARS-CoV-2 NT50 in children 5 to <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), as presented in Table 22.

Table 22: Summary of geometric mean ratio for 50% neutralising titre – Comparison of children 5 to <12 years of age (Study C4591007) to participants 16 to 25 years of age (Study C4591001) – participants without* evidence of infection up to 1 month after Dose 2 – evaluable immunogenicity population

		COMIRNATY (tozinameran)		5 to <12 years/ 16 to 25 years	
		10 microgram/dose 5 to <12 years n^a=264	30 microgram/dose 16 to 25 years n^a=253		
Assay	**Time point[b]**	**GMT[c] (95% CI[c])**	**GMT[c] (95% CI[c])**	**GMR[d] (95% CI[d])**	**Met immunobridging objective[e] (Y/N)**
SARS-CoV-2 neutralisation assay - NT50 (titre)[f]	1 month after Dose 2	1197.6 (1106.1, 1296.6)	1146.5 (1045.5, 1257.2)	1.04 (0.93, 1.18)	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.

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

a. n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
b. Protocol-specified timing for blood sample collection.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
d. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (Group 1[5 to < 12 years of age] - Group 2 [16 to 25 years of age]) and the corresponding CI (based on the Student t distribution).
e. Immunobridging is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the point estimate of the GMR is ≥0.8.
f. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralisation Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralisation is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralised.

Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, 99.2% of children 5 to <12 years of age and 99.2% of participants 16 to 25 years of age had a seroresponse from before vaccination to 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%) as presented in Table 23.

Table 23: Difference in percentages of participants with seroresponse – participants without evidence of infection up to 1 month after Dose 2 – immunobridging subset – Phase 2/3 – comparison of 5 to <12 years of age to Study C4591001 Phase 2/3 16 to 25 years of age – evaluable immunogenicity population

		COMIRNATY (tozinameran)		5 to <12 years/ 16 to 25 years	
		10 microgram/dose 5 to <12 years Na=264	30 microgram/dose 16 to 25 years Na=253		
Assay	Time pointb	nc (%) (95% CId)	nc (%) (95% CId)	Difference %e (95% CIf)	Met immunobridging objectiveg (Y/N)
SARS-CoV-2 neutralisation assay – NT50 (titre)h	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: LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralising titre 50; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

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 ≥4 × LLOQ is considered a seroresponse.

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

a. N = number of participants with valid and determinate assay results both before vaccination and at 1 month after Dose 2. These values are the denominators for the percentage calculations.
b. Protocol-specified timing for blood sample collection.
c. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.
d. Exact 2-sided CI based on the Clopper and Pearson method.
e. Difference in proportions, expressed as a percentage (Group 1 [5 to < 12 years of age] – Group 2 [16 to 25 years of age]).
f. 2-Sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
g. Immunobridging is declared if the lower bound of the 2-sided 95% CI for the difference in proportions is greater than -10.0%.
h. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralisation Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralisation is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralised.

Efficacy and immunogenicity in infants and children 6 months to <5 years of age – 3-dose primary course

A preliminary descriptive efficacy analysis was performed across the combined population of participants 6 months to <5 years of age based on cases confirmed among 992 participants in the COMIRNATY (tozinameran) group and 464 participants in the placebo group who received all 3 doses of study intervention during the blinded follow-up period. The observed vaccine efficacy from at least 7 days after Dose 3 to the cutoff date (29 April 2022) was 80.3% (2-sided 95% CI: 13.9, 96.7) based on 3 cases in the COMIRNATY (tozinameran) group and 7 cases in the placebo group, adjusted for surveillance time (noting 2:1 randomisation ratio). Vaccine efficacy analyses were associated with wide confidence intervals. In addition, the preliminary nature of the data (prespecified number of cases not yet reached in Study C4591007) may preclude any definitive vaccine efficacy conclusions.

Children 2 to <5 years of age – after 3 doses
A descriptive efficacy analysis of Study C4591007 has been performed in participants 2 to <5 years of age. This analysis evaluated confirmed symptomatic COVID-19 cases accrued up to a data cutoff date of 29 April 2022.

Dosing intervals: In the evaluable efficacy population, there was a wide dosing interval range between COMIRNATY (tozinameran) Dose 2 and Dose 3 for participants 2 to <5 years of age was 6.0 to 34.1 weeks with a median interval of 11.0 weeks.

The descriptive vaccine efficacy results after Dose 3 in participants 2 to <5 years of age are presented in Table 24.

Table 24: Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 3 - Phase 2/3 – Participants 2 to <5 years of age – Dose 3 all-available efficacy population (blinded follow-up period)

	COMIRNATY (tozinameran) 3 micrograms/dose N[a]=606 Cases n1[b] Surveillance time[c] (n2[d])	**Placebo N[a]=280 Cases n1[b] Surveillance time[c] (n2[d])**	**Vaccine efficacy (%) (95% CI[e])**
First COVID-19 occurrence from 7 days after Dose 3	2 0.056 (481)	5 0.025 (209)	82.3 (-8.0, 98.3)

Abbreviation: VE = vaccine efficacy.
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; diarrhea; vomiting; inability to eat/poor feeding).
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.

Additional evaluation of vaccine efficacy for cases confirmed at least 7 days after Dose 2 and before Dose 3 was performed. In the evaluable efficacy population in participants without prior evidence of SARS-CoV-2 infection before or during the vaccination regimen the observed vaccine efficacy from at least 7 days after Dose 2 and before Dose 3 was 35.9% (2-sided 95% CI: 11.0, 53.7). The vaccine efficacy in participants with or without prior evidence of SARS-CoV-2 infection before or during the vaccination regimen was similar.

Analysis of COVID-19 cases that excluded those involving coinfection with other respiratory pathogens did not meaningfully impact the estimated vaccine efficacy in this population.

Severe COVID-19 criteria (as described in the protocol, based on FDA definition and modified for children) were fulfilled for 7 cases [6 COMIRNATY (tozinameran) and 1 placebo] among participants 2 to <5 years of age, of which 5 of the 6 cases in the COMIRNATY group fulfilled a single criterion of increased heart rate or respiratory rate and 1 case in the placebo group fulfilled a single criterion of decreased peripheral oxygen saturation (88% on room air). None of the cases accrued met criteria for multisystem inflammatory syndrome in children (MIS-C).

Immunogenicity analyses have been performed in the immunobridging subset of 143 C4591007 participants 2 to <5 years of age without evidence of infection up to 1 month after Dose 3 based on a data cutoff date of 29 April 2022.

SARS-CoV-2 50% neutralising antibody titres (NT50) were compared between an immunogenicity subset of Phase 2/3 participants 2 to <5 years of age from C4591007 at 1 month after the 3-dose primary course and a randomly selected subset from C4591001 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 2 to <5 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 (Table 25 and Table 26, respectively).

Table 25: SARS-CoV-2 GMTs (NT50) at 1 month after vaccination course – immunobridging subset - participants 2 to <5 years of age (C4591007) 1 month after Dose 3 and participants 16 to 25 years of age (C4591001) 1 month after Dose 2 – without evidence of SARS-CoV-2 infection – evaluable immunogenicity population

	COMIRNATY (tozinameran)		
	3 micrograms/dose 2 to <5 years of age (1 month after Dose 3) n[a]=143	**30 micrograms/dose 16 to 25 years of age (1 month after Dose 2) n[a]=170**	**GMR (95%CI) (2 to <5 years of age/16 to 25 years of age)[c,d]**
Assay	**GMT[b] (95% CI[b])**	**GMT[b] (95% CI[b])**	
SARS-CoV-2 neutralisation assay - NT50 (titre)[e]	1535.2 (1388.2, 1697.8)	1180.0 (1066.6, 1305.4)	1.30 (1.13, 1.50)

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 after Dose 2 (C4591001) or 1 month after Dose 3 (C4591007) blood sample collection)] of past SARS-CoV-2 infection [(i.e., N-binding antibody [serum] negative at Dose 1, Dose 3 (C4591007) and 1 month after Dose 2 (C4591001) or 1 month after Dose 3 (C4591007), SARS-CoV-2 not detected by NAAT [nasal swab] at Dose 1, Dose 2, and Dose 3 (C4591007) study visits, and negative NAAT (nasal swab) at any unscheduled visit up to 1 month after Dose 2 (C4591001) or 1 month after Dose 3 (C4591007) blood collection)] and had no medical history of COVID-19 were included in the analysis.

a. n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
b. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.

c. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (2 to <5 years of age minus 16 to 25 years of age) and the corresponding CI (based on the Student t distribution).
d. Immunobridging is declared if the lower bound of the 2-sided 95% CI for the GMR ratio is greater than 0.67 and the point estimate of the GMR is ≥0.8.
e. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralisation Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralisation is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralised.

Table 26: Difference in percentages of participants with seroresponse at 1 month after vaccination course – immunobridging subset –participants 2 to <5 years of age (C4591007) 1 month after Dose 3 and participants 16 to 25 years of age (C4591001) 1 month after Dose 2 without evidence of infection – evaluable immunogenicity population

	COMIRNATY (tozinameran)		Difference in seroresponse rates %[d] (95% CI[e]) (2 to <5 years of age minus 16 to 25 years of age)[f]
	3 micrograms/dose 2 to <5 years of age (1 month after Dose 3) N[a]=141	30 micrograms/dose 16 to 25 Years of age (1 month after Dose 2) N[a]=170	
Assay	n[b] (%) (95% CI[c])	n[b] (%) (95% CI[c])	
SARS-CoV-2 neutralisation assay - NT50 (titre)[g]	141 (100.0) (97.4, 100.0)	168 (98.8) (95.8, 99.9)	1.2 (-1.5, 4.2)

Abbreviations: LLOQ = lower limit of quantitation; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein–binding; NT50 = 50% neutralising titre 50; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
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 ≥4 × LLOQ is considered a seroresponse.
Note: Participants who had no serological or virological evidence (up to 1 month after Dose 2 [(C4591001) or 1 month after Dose 3 (C4591007) blood sample collection)[of past SARS-CoV-2 infection [(i.e., N-binding antibody [serum] negative at pre-Dose 1, pre-Dose 3 (C4591007) and 1 month after Dose 2 (C4591001) or 1 month after Dose 3 (C4591007), SARS-CoV-2 not detected by NAAT [nasal swab] at pre-Dose 1, pre-Dose 2, and pre-Dose 3 (C4591007) study visits, and negative NAAT (nasal swab) at any unscheduled visit up to 1 month after Dose 2 (C4591001) or 1 month after Dose 3 (C4591007) blood collection)] and had no medical history of COVID-19 were included in the analysis.
a. N = number of participants with valid and determinate assay results both before vaccination and at 1 month after Dose 2. These values are the denominators for the percentage calculations.
b. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.
c. Exact 2-sided CI based on the Clopper and Pearson method.
d. Difference in proportions, expressed as a percentage (2 to <5 years of age minus 16 to 25 years of age).
e. 2-sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
f. Immunobridging 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.
g. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralisation Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralisation is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralised.

Omicron and Delta variants

Using a non-validated fluorescence focus reduction neutralisation test assay against the Omicron variant of SARS-CoV-2 (BA.1), the NT50 GMT at 1 month after Dose 3 among a subset of 34 study participants without evidence of prior SARS-CoV-2 infection (82.5 [2-sided

95% CI: 55.4, 122.9]) was increased compared to the NT50 GMT before Dose 3 (14.0 [2-sided 95% CI: 10.6, 18.5]).

By comparison, in the same subset of 34 study participants without evidence of prior SARS-CoV-2 infection, there were notable higher NT50 GMTs at 1 month after Dose 3 against the Delta variant and wildtype SARS-CoV-2 (471.4 [2-sided 95% CI: 341.2, 651.1] and 471.4 [2-sided 95% CI: 344.6, 644.8], respectively). The NT50 GMTs before Dose 3 against the Delta variant and wildtype SARS-CoV-2 were 68 [2-sided 95% CI: 49.5, 93.3] and 70.1 [2-sided 95% CI: 51.1, 96], respectively.

An additional descriptive immunogenicity analysis was performed for participants 2 to <5 years of age who received a 3-dose course of COMIRNATY (tozinameran) in Phase 2/3 C4591007, compared with a subset of participants 18 to 50 years of age in Phase 3 Study C4591017 who had received a 2-dose primary course followed by a booster dose of COMIRNATY 30 micrograms. The comparator group (participants 18 to 50 years of age) in this analysis had a similar interval between COMIRNATY (tozinameran) Dose 2 and Dose 3 (median 13.0 weeks) as the participants 2 to <5 years of age (median 10.6 weeks). Among 34 participants 2 to <5 years of age without evidence of prior SARS-CoV-2 infection who received 3 doses of COMIRNATY 3 micrograms, neutralising GMTs were 114.3 at 1-month post-Dose 3. Among 27 participants 18 to 50 years of age without evidence of prior SARS-CoV-2 infection who received 3 doses of COMIRNATY 30 micrograms, Omicron neutralising GMTs were 164.2 at 1-month post Dose 3.

Infants 6 months to <2 years of age – after 3 doses

A descriptive efficacy analysis of C4591007 has been performed in participants 6 months to <2 years of age. This analysis evaluated confirmed symptomatic COVID-19 cases accrued up to a data cutoff date of 29 April 2022.

Dosing intervals: In the evaluable efficacy population, there was a wide dosing interval range between COMIRNATY (tozinameran) Dose 2 and Dose 3 for participants 6 months to <2 years of age was 8.0 to 31.9 weeks with a median interval of 16.0 weeks.

The descriptive vaccine efficacy results after dose 3 in participants 6 months to <2 years of age are presented in Table 27.

Table 27: Vaccine efficacy – first COVID-19 occurrence from 7 days after Dose 3 – phase 2/3 – participants 6 months to <2 years of age – Dose 3 all-available efficacy population (blinded follow-up period)

	COMIRNATY (tozinameran) 3 micrograms/dose N[a]=386 Cases n1[b] Surveillance time[c] (n2[d])	**Placebo N[a]=184 Cases n1[b] Surveillance time[c] (n2[d])**	**Vaccine efficacy (%) (95% CI[e])**
First COVID-19 occurrence from 7 days after Dose 3	1 0.030 (277)	2 0.015 (139)	75.5 (-370.1, 99.6)

Abbreviation: VE = vaccine efficacy.

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;

diarrhea; vomiting; inability to eat/poor feeding).

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.

Additional evaluation of vaccine efficacy for cases confirmed at least 7 days after Dose 2 and before Dose 3 was performed. In the evaluable efficacy population in participants without prior evidence of SARS-CoV-2 infection before or during the vaccination regimen the observed vaccine efficacy from at least 7 days after Dose 2 and before Dose 3 was 16.1% (2-sided 95% CI: -24.9, 43.1). The vaccine efficacy in participants with or without prior evidence of SARS-CoV-2 infection before or during the vaccination regimen was similar.

Analysis of COVID-19 cases that excluded those involving coinfection with other respiratory pathogens did not meaningfully impact the estimated vaccine efficacy in this population.

One participant in the placebo group, had confirmed COVID-19 which met a single severe case criterion described in the protocol (increased heart rate [172 bpm]). None of the cases accrued met criteria for multisystem inflammatory syndrome in children (MIS-C).

Immunogenicity analyses have been performed in the immunobridging subset of 82 C4591007 participants 6 months to <2 years of age without evidence of infection up to 1 month after Dose 3 based on a data cutoff date of 29 April 2022.

SARS-CoV-2 50% neutralising antibody titres (NT50) 1 month after the vaccination course were compared between an immunogenicity subset of Phase 2/3 participants 6 months to <2 years of age from C4591007 and a randomly selected subset from C4591001 Phase 2/3 participants 16 to 25 years of age, using a microneutralisation assay against the reference strain (USA_WA1/2020). The primary immunobridging analyses compared the geometric mean titres (using a 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 months to <2 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 (Table 28 and Table 29, respectively).

Table 28: SARS-CoV-2 GMTs (NT50) at 1 month after vaccination course – immunobridging subset - participants 6 months to <2 years of age (C4591007) 1 month after Dose 3 and participants 16 to 25 years of age (C4591001) 1 month after Dose 2 – without evidence of SARS-CoV-2– evaluable immunogenicity population

	COMIRNATY (tozinameran)		
	3 micrograms/dose 6 months to <2 years of age (1 month after Dose 3) n[a]=82	**30 micrograms/dose 16 to 25 years of age (1 month after Dose 2) n[a]=170**	**GMR (95%CI) (6 months to <2 years of age/16 to 25 years of age)[c,d]**
Assay	**GMT[b] (95% CI[b])**	**GMT[b] (95% CI[b])**	

SARS-CoV-2 neutralisation assay - NT50 (titre)[e]	1406.5 (1211.3, 1633.1)	1180.0 (1066.6, 1305.4)	1.19 (1.00, 1.42)

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 after Dose 2 (C4591001) or 1 month after Dose 3 (C4591007) blood sample collection)] of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Dose 1, Dose 3 (C4591007) and 1 month after Dose 2 (C4591001) or 1 month after Dose 3 (C4591007), SARS-CoV-2 not detected by NAAT [nasal swab] at Dose 1, Dose 2, and Dose 3 (C4591007) study visits, and negative NAAT (nasal swab) at any unscheduled visit up to 1 month after Dose 2 (C4591001) or 1 month after Dose 3 (C4591007) blood collection)] and had no medical history of COVID-19 were included in the analysis.

a. n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
b. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titre titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
c. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (6 months to <2 years of age minus 16 to 25 years of age) and the corresponding CI (based on the Student t distribution).
d. Immunobridging is declared if the lower bound of the 2-sided 95% CI for the GMR ratio is greater than 0.67 and the point estimate of the GMR is ≥0.8.
e. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralisation Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralisation is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralised.

Table 29: Difference in percentages of participants with seroresponse at 1 month after vaccination course – immunobridging subset – participants 6 months to <2 years of age (C4591007) 1 month after Dose 3 and participants 16 to 25 years of age (C4591001) to 1 month after Dose 2 without evidence of infection – evaluable immunogenicity population

	COMIRNATY (tozinameran)		**Difference in seroresponse rates %[d] (95% CI[e]) (6 months to <2 years of age minus 16 to 25 years of age)[f]**
	3 micrograms/dose 6 to 23 months of age (1 month after Dose 3) N[a]=80	**30 micrograms/dose 16 to 25 years of age (1 month after Dose 2) N[a]=170**	
Assay	**n[b] (%) (95% CI[c])**	**n[b] (%) (95% CI[c])**	
SARS-CoV-2 neutralisation assay - NT50 (titre)[g]	80 (100.0) (95.5, 100.0)	168 (98.8) (95.8, 99.9)	1.2 (-3.4, 4.2,)

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

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 ≥4 × LLOQ is considered a seroresponse.

Note: Participants who had no serological or virological evidence [(up to 1 month after Dose 2 (C4591001) or 1 month after Dose 3 (C4591007) blood sample collection) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at pre-Dose 1, Dose 3 (C4591007) and 1 month after Dose 2 (C4591001) or 1 month after Dose 3 (C4591007), SARS-CoV-2 not detected by NAAT [nasal swab] at pre-Dose 1, pre-Dose 2, and pre-Dose 3 (C4591007) study visits, and negative NAAT (nasal swab) at any unscheduled visit up to 1 month after Dose 2 (C4591001) or 1 month after Dose 3 (C4591007) blood collection)] and had no medical history of COVID-19 were included in the analysis.

a. N = number of participants with valid and determinate assay results both before vaccination and at 1 month after Dose 2. These values are the denominators for the percentage calculations.
b. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.
c. Exact 2-sided CI based on the Clopper and Pearson method.
d. Difference in proportions, expressed as a percentage (6 months to <2 years of age minus 16 to 25 years of age).
e. 2-sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
f. Immunobridging 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.
g. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralisation Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralisation is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralised.

Omicron and Delta variants

Using a non-validated fluorescence focus reduction neutralisation test assay against the Omicron variant of SARS-CoV-2 (BA.1), the NT50 GMT at 1 month after Dose 3 among a subset of 32 study participants without evidence of prior SARS-CoV-2 infection (127.5 [2-sided 95% CI: 90.2, 180.1]) was increased compared to the NT50 GMT before Dose 3 (16.3 [2-sided 95% CI: 12.8, 20.8]).

By comparison, in the same subset of 32 study participants without evidence of prior SARS-CoV-2 infection, there were notable higher NT50 GMTs at 1 month after Dose 3 against the Delta variant and wildtype SARS-CoV-2 (606.3 [2-sided 95% CI: 455.5, 806.9] and 640.0 [2-sided 95% CI: 502.6, 815.0], respectively). The NT50 GMTs before Dose 3 against the Delta variant and wildtype SARS-CoV-2 were 94.1 [2-sided 95% CI: 67.9, 130.5] and 103.7 [2-sided 95% CI: 78.4, 137.3], respectively.

An additional descriptive immunogenicity analysis was performed for participants 6 months to <2 years of age who received a 3-dose course of COMIRNATY (tozinameran) in Phase 2/3 C4591007, compared with a subset of participants 18 to 50 years of age in Phase 3 Study C4591017 who had received a 2-dose primary course followed by a booster dose of COMIRNATY 30 micrograms. The comparator group (participants 18 to 50 years of age) in this analysis had a similar interval between COMIRNATY (tozinameran) Dose 2 and Dose 3 (median 13.0 weeks) as the participants 6 months to <2 years of age (median 12.9 weeks). Among 32 participants 6 months to <2 years of age without evidence of prior SARS-CoV-2 infection who received 3 doses of COMIRNATY 3 micrograms, Omicron neutralising GMTs were 128.8 at 1-month post-Dose 3. Among 27 participants 18 to 50 years of age without evidence of prior SARS-CoV-2 infection who received 3 doses of COMIRNATY (tozinameran) 30 micrograms, Omicron neutralising GMTs were 164.2 at 1-month post Dose 3.

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

Effectiveness of a booster dose of COMIRNATY (tozinameran) was based on an assessment of 50% neutralising titres (NT50) against SARS-CoV-2 (USA_WA1/2020). In Study C4591001, analyses of NT50 1 month after the booster dose compared to 1 month after the primary series in individuals 18 to 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 GMR and difference in seroresponse rates. Seroresponse for a participant was defined as achieving a ≥4-fold rise in NT50 from baseline (before Dose 1), These analyses are summarised in Table 30.

Table 30. SARS-CoV-2 Neutralisation 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 to 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% neutralising titre (GMT[b])	212[a]	2466.0[b] (2202.6, 2760.8)	750.6[b] (656.2, 858.6)	3.29[c] (2.77, 3.90)	Y[d]
Seroresponse rate (%) for 50% neutralising titre†	200[e]	199[f] 99.5% (97.2%, 100.0%)	196[f] 98.0% (95.0%, 99.5%)	1.5%[g] (-0.7%, 3.7%[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% neutralising 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 Microneutralisation Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralisation is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralised.

* Participants who had no serological or virological evidence (up to 1 month after receipt of a booster dose of COMIRNATY (tozinameran)) 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 (tozinameran) 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 (tozinameran), had at least 1 valid and determinate immunogenicity result after booster dose from a blood collection within an appropriate window (within 28 to 42 days after the booster dose), and had no other important protocol deviations as determined by the clinician.

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

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

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

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

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

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

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

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

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

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

An interim efficacy analysis of Study C4591031, a placebo-controlled booster study, was performed in approximately 10,000 participants 16 years of age and older who were recruited from Study C4591001, evaluated confirmed COVID-19 cases accrued from at least 7 days after booster vaccination up to a data cut-off date of 8 February 2022 (a period when Delta and then Omicron was the predominant variant), which represents a median of 2.8 months (range 0.3 to 7.5 months) post-booster follow-up. Vaccine efficacy of the COMIRNATY (tozinameran) 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 is presented in Table 31.

Table 31: Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Booster Vaccination – Participants 16 Years of Age and Older Without Evidence of Infection and Participants With or Without Evidence of Infection Prior to 7 Days After Booster Vaccination – Evaluable Efficacy Population

First COVID-19 occurrence from 7 days after booster dose in participants without evidence of prior SARS-CoV-2 infection*			
	COMIRNATY (tozinameran) N[a]=4689 Cases n1[b] Surveillance Time[c] (n2[d])	**Placebo N[a]=4664 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	63 1.098 (4639)	148 0.932 (4601)	63.9 (51.1, 73.5)
First COVID-19 occurrence from 7 days after booster dose in participants with or without evidence of prior SARS-CoV-2 infection			
	COMIRNATY (tozinameran) N[a]=4977 Cases n1[b] Surveillance Time[c] (n2[d])	**Placebo N[a]=4942 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	67 1.173 (4903)	150 0.989 (4846)	62.4 (49.5, 72.2)

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; diarrhea; vomiting).

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

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

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

c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after the booster vaccination to the end of the surveillance period.

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

e. Relative vaccine efficacy of the COMIRNATY booster group relative to the placebo group (non-booster).

f. Two-sided confidence interval (CI) for relative vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.

Immunogenicity in children 5 to <12 years of age – after booster dose

In a subset from C4591007, a total of 123 children 5 to <12 years of age received a booster dose of COMIRNATY (tozinameran) 10 micrograms after completing the primary series. All participants in the 3-Dose immunogenicity subset, received the booster dose 7 - < 9 months after Dose 2, (n = 37 [30.1%] at 7 - < 8 months and n = 86 [69.9%] at 8 - < 9 months).

Effectiveness of a booster dose of COMIRNATY (tozinameran) was based on an assessment of 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 an increase in GMTs in individuals 5 to <12 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the booster dose. This analysis is summarised in Table 32.

Table 32: Summary of Geometric Mean Titres – NT50 – Participants Without Evidence of Infection – Phase 2/3 – Immunogenicity Set – 5 to <12 Years of Age – Evaluable Immunogenicity Population

		COMIRNATY (tozinameran) 10 micrograms/Dose					
		3-Dose Set		2-Dose Set		Total	
Assay	Dose/ Sampling Time Point[a]	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])
SARS-CoV-2 neutralisation assay - NT50 (titre)	Dose 1 Prevax	79	20.5 (20.5, 20.5)	67	20.5 (20.5, 20.5)	146	20.5 (20.5, 20.5)
	1 month after Dose 2	29	1659.4 (1385.1, 1988.0)	67	1110.7 (965.3, 1278.1)	96	1253.9 (1116.0, 1408.9)
	Dose 3 Prevax	67	271.0 (229.1, 320.6)	-	-	67	271.0 (229.1, 320.6)
	1 month after Dose 3	67	2720.9 (2280.1, 3247.0)	-	-	67	2720.9 (2280.1, 3247.0)

Abbreviations: CI = confidence interval; 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; Prevax = before vaccination; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Three-dose immunogenicity set included the first 130 participants who received Dose 3 and completed 1-month post–Dose 3 visit prior to March 15, 2022. Among those, 30 had blood sample collection at 1-month post-Dose 2. Two-dose immunogenicity set included an extra 67 participants randomly selected from previous Dose-2 evaluable immunogenicity population and without evidence of infection up to 1-month post–Dose 2 subset used for 2-dose immunobridging analysis.

Note: Participants included in this analysis had no serological or virological evidence of past SARS-CoV-2 infection up to the 1-month post–Dose 2 (for 1-month post–Dose 2 time point) or 1-month post–Dose 3 (for pre–Dose 3 and 1-month post–Dose 3 time point) study blood sample collection. Having no evidence of past SARS-CoV-2 infection up to 1-month post–Dose 2 was defined as having a negative N-binding antibody (serum) result at the Dose 1 and 1-month post–Dose 2 study visits; a negative NAAT (nasal swab) result at the Dose 1 and Dose 2 study visits and any unscheduled visit prior to the 1-month post–Dose 2 blood sample collection; and no medical history of COVID-19. Having no evidence of past SARS-CoV-2 infection up to 1-month post-Dose 3 was defined as having a negative N-binding antibody (serum) result at the Dose 1, 1-month post–Dose 2 (if available), Dose 3, and 1-month post–Dose 3 study visits; a negative NAAT (nasal swab) result at the Dose 1, Dose 2, and Dose 3 study visits and any unscheduled visit prior to the 1-month post–Dose 3 blood sample collection; and no medical history of COVID-19.

a. Protocol-specified timing for blood sample collection.
b. n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Genotoxicity/Carcinogenicity

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

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)
Distearoylphosphatidylcholine (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 4.2 Dose and method of administration.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

Unopened vial

COMIRNATY Original/Omicron BA.4-5 may be received frozen at -90°C to -60°C or at -25°C to -15°C. Frozen vaccine can be stored either at -90°C to -60°C or 2°C to 8°C upon receipt.

Once removed from frozen storage, the unopened vial may be stored refrigerated at 2°C to 8°C for a single period of up to 10 weeks within the approved shelf life.

Upon moving the product 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. Check that the expiry date on the outer carton has been updated to reflect the refrigerated expiry date and that the original expiry date has been crossed out.

When stored frozen at -90°C to -60°C, the vaccine can be thawed at either 2°C to 8°C or at temperatures up to 30°C.

Vaccine may be stored at temperatures between 8°C to 30°C for up to 24 hours, including any time within these temperatures following first puncture.

Thawed vials can be handled in room light conditions.

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

COMIRNATY Original/Omicron BA.4-5 – Suspension for Injection (Grey or Blue Cap)

Opened vial

Chemical and physical in-use stability has been demonstrated for 12 hours at 2ºC to 30ºC. From a microbiological point of view, unless the method of opening precludes the risks of microbial contamination, the product should be used immediately after the first puncture. If not used immediately, in-use storage times and conditions cannot be longer than 12 hours at 2°C to 30°C.

COMIRNATY Original/Omicron BA.4-5 - Concentrated Suspension for Injection (Orange or Maroon Cap)

Diluted medicinal product

Chemical and physical in-use stability has been demonstrated for 12 hours at 2ºC to 30ºC, after dilution with sodium chloride 9 mg/mL (0.9%) solution for injection. 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 cannot be longer than 12 hours at 2°C to 30°C.

6.4 Special precautions for storage

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.

When stored frozen at -90°C to -60°C, the vaccine can be thawed at either 2°C to 8°C or at room temperature (up to 30°C). For detailed instructions see Section 4.2 Dose and method of administration, Handling instructions (Handling prior to use).

Once thawed, the vaccine cannot be re-frozen.

Thawed vials can be handled in room light conditions.

For storage conditions after thawing and dilution of the medicinal product, see Section 6.3 Shelf life.

For additional advice on storing COMIRNATY Original/Omicron BA.4-5, contact Pfizer Australia on 1800 675 229.

6.5 Nature and contents of container

COMIRNATY Original/Omicron BA.4-5 – Suspension for injection (Grey or Blue cap): 2 mL clear vial (Type I glass) with a stopper (synthetic bromobutyl rubber) and a Grey or Blue flip-off plastic cap with aluminium seal. Each vial contains either 1 or 6 doses, see Section 4.2 Dose and method of administration.

- Light Grey or Light Blue cap: single dose vial
- Dark Grey or Dark Blue cap: 6 dose multidose vial

COMIRNATY Original/Omicron BA.4-5 – Concentrated Suspension for injection (Orange or Maroon cap): 2 mL clear vial (Type I glass) with a stopper (synthetic bromobutyl rubber) and an Orange or Maroon flip-off plastic cap with aluminium seal. Each vial contains 10 doses after dilution, see Section 4.2 Dose and method of administration.

- Orange or Maroon cap: 10 dose multidose vial after dilution

Pack size: 10 vials, 195 vials

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

CAS number

2417899-77-3

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizermedinfo.com.au

9. DATE OF FIRST APPROVAL

Aust R 400874: 23 January 2023

Aust R 413718, 412350, 413720 & 413719: 21 December 2023

Aust R 417266: TBD

10. DATE OF REVISION

TBD

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Summary Table of Changes

Section changed	Summary of new information
2, 3, 4.1, 4.2, 4.4, 4.8, 5.1, 6.3 and 6.5	Extension of indication for use in infants and children 6 months to <5 years of age, and introduction of new presentation (1.5/1.5 micrograms per dose strength) for the new target population. Inclusion of related dosage & administration, handling instruction, safety and immunogenicity information for the new target population.