▼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® Omicron XBB.1.5 (raxtozinameran) COVID-19 VACCINE

1. NAME OF THE MEDICINE

Raxtozinameran

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Raxtozinameran is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Omicron XBB.1.5).

COMIRNATY Omicron XBB.1.5			
Age group	12 years and older	5 to <12 years	6 months to <5 years
Strength per dose	30 micrograms	10 micrograms	3 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	**419370**	**419330**	**419331**	**419371**	**419372**	**419332**	**428610**
Cap & Label colour code	Light Grey	Dark Grey	Orange	Light Blue	Dark Blue	Maroon	Yellow
Pharmaceutical form	Suspension for injection		Concentrate for suspension for injection	Suspension for injection		Concentrate for suspension for injection	
Strength per dose	30 micrograms (0.3 mL dose)		10 micrograms (0.2 mL dose)	10 micrograms (0.3 mL dose)		3 micrograms (0.2 mL dose)	3 micrograms (0.3 mL dose)
Fill volume	0.48 mL	2.25 mL	1.3 mL	0.48 mL	2.25 mL	0.4 mL	0.48 mL
No. of doses per vial	1	6	10	1	6	10	3
Dilution	Do not dilute		Requires dilution	Do not dilute		Requires dilution	

COMIRNATY Omicron XBB.1.5 (Grey, Orange and Maroon cap) is a white to off-white frozen suspension.

COMIRNATY Omicron XBB.1.5 (Blue and yellow cap) is a clear to slightly opalescent solution.

COMIRNATY Omicron XBB.1.5 – Single dose Glass Prefilled Syringes and Single dose Plastic Prefilled Syringes, 30 micrograms, for 12 years and older is a white to off-white suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

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)**
3 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.
	Yellow	0.3 mL	
10 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	
30 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/COMIRNATY Omicron XBB.1.5 should continue to receive COMIRNATY Omicron XBB.1.5 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 Omicron XBB.1.5 should not be mixed in the same syringe with any other vaccines or medicinal products.

For precautions to be taken before administering COMIRNATY Omicron XBB.1.5, see Section 4.4 Special warnings and precautions for use.

COMIRNATY Omicron XBB.1.5 - Suspension for Injection

Vials of COMIRNATY Omicron XBB.1.5 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

In order to extract six doses from a single vial, low dead-volume syringes and/or needles should be used. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial. Irrespective of the type of syringe and needle:

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

For instructions on the handling, thawing and dose preparation of the vaccine before administration see Handling instructions.

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 Yellow	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 Omicron XBB.1.5 - Suspension for Injection

Preparation for administration

COMIRNATY Omicron XBB.1.5 Suspension for Injection should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared suspension.

Vials of COMIRNATY Omicron XBB.1.5 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 Omicron XBB.1.5 – Concentrated Suspension for Injection

Preparation for administration

COMIRNATY Omicron XBB.1.5 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 Omicron XBB.1.5 Concentrated Suspension for Injection contain:

- *Orange or Maroon cap:* 10 doses of 0.2 mL of vaccine after dilution
- *Yellow cap:* 3 doses of 0.3 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.
    - *Yellow cap vials*: Prior to dilution, the vaccine is a clear to slightly opalescent solution.

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
    - *Yellow cap vials:* 1.1 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
    - *Yellow cap vials:* 1.1 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.
- *Yellow cap vials: :* After mixing, the vaccine should present as a clear to slightly opalescent dispersion with no particulates visible. Do not use the vaccine if particulates or discoloration are present.

- 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.
  - *Yellow cap multidose vials (3 doses per vial):*
    - Each dose must contain 0.3 mL of vaccine.
    - Standard syringes can be used.
- If the amount of vaccine remaining in the vial cannot provide a full dose, discard the vial and any excess volume.

COMIRNATY Omicron XBB.1.5 – Single dose Glass Prefilled Syringes, 30 micrograms 12 years and older (Do not dilute)

- If glass prefilled syringe has been frozen, discard.
- Do not shake.
- Remove tip cap by slowly turning the cap counterclockwise while holding the luer lock and attach a sterile needle.
- Product is for single use in one patient only. Discard any residue.

COMIRNATY Omicron XBB.1.5 – Single dose Plastic Prefilled Syringes, 30 micrograms, 12 years and older (Do not dilute)

- If syringes are frozen, thaw syringe in the carton in the refrigerator [2°C to 8°C] or at room temperature [up to 30°C]. Do not remove syringe from carton to thaw.
- Do not shake.
- Remove tip cap and attach a sterile needle.
- Product is for single use in one patient only. Discard any residue.

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 COMIRNATY Omicron XBB.1.5.

The individual should be kept under close observation for at least 15 minutes following vaccination. A second dose of COMIRNATY Omicron XBB.1.5 should not be given to those who have experienced anaphylaxis to the first dose of COMIRNATY/COMIRNATY Omicron XBB.1.5.

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, COMIRNATY Omicron XBB.1.5 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 COMIRNATY/COMIRNATY Omicron XBB.1.5 has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of COMIRNATY Omicron XBB.1.5 may be lower in immunosuppressed individuals.

Duration of protection

The duration of protection afforded by COMIRNATY/COMIRNATY Omicron XBB.1.5 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 Omicron XBB.1.5 may not protect all vaccine recipients. Individuals may not be fully protected until 7 days after their primary course of the vaccine.

Use in the elderly

Clinical studies of COMIRNATY (tozinameran) include participants 65 years of age and older and their data contributes to the overall assessment of safety and efficacy. 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.

The safety of a booster dose of COMIRNATY in individuals 65 years of age and older is based on safety data in 12 booster dose recipients 65 to 85 years of age in Study C4591001, 306 booster dose recipients 18 to 55 years of age in Study C4591001, and 1,175 booster dose recipients 65 years of age and older in Study C4591031. The effectiveness of a booster dose of

COMIRNATY in individuals 65 years of age and older is based on effectiveness data in 306 booster dose recipients 18 to 55 years of age in Study C4591001, and an efficacy analysis from participants 16 years of age and older in 9,945 participants in Study C4591031.

Paediatric use

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

Limited safety and effectiveness data is available for 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 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 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

COMIRNATY (30 micrograms/dose only) may be administered concomitantly with seasonal influenza vaccine (see Section 5.1 Pharmacodynamic properties, Concomitant vaccine administration with influenza vaccine).

Different injectable vaccines should be given at different injection sites.

Do not mix COMIRNATY with other vaccines or products in the same syringe.

4.6 Fertility, pregnancy and lactation

Effects on fertility

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 Omicron XBB.1.5 during pregnancy. However, a large amount of information from pregnant women vaccinated with the initially approved COMIRNATY vaccine during the second and third trimester have not shown negative effects on the pregnancy or the newborn baby. While information on effects on

pregnancy or the newborn baby after vaccination during the first trimester is limited, no change to the risk for miscarriage has been seen.

There is limited experience with use of COMIRNATY in pregnant women. 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 Omicron XBB.1.5 in pregnancy can 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 Omicron XBB.1.5 during breast-feeding. COMIRNATY Omicron XBB.1.5 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 has no, or negligible, influence on the ability to drive, cycle and use machines. However, some of the effects mentioned under Section 4.8 Adverse effects (undesirable effects) may temporarily affect the ability to drive, cycle or use machines.

4.8 Adverse effects (undesirable effects)

Summary of safety profile

The safety of COMIRNATY Omicron XBB.1.5 is inferred from safety data of the prior COMIRNATY (tozinameran) vaccines.

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 3,109 children 5 to <12 years of age, 2,368 participants 2 to <5 years of age and 1,458 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, 2,408 participants 5 to <12 years of age received a booster dose of COMIRNATY (tozinameran) at least 5 months (range 5.3 to 19.4 months) after completing the primary series. 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.

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); 773 placebo] were followed for ≥ 4 months after the second dose of COMIRNATY (tozinameran).

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, 4,647 children [3,109 COMIRNATY (tozinameran) 10 micrograms; 1,538 placebo] were 5 to <12 years of age. Of these, 2,206 [1,481 COMIRNATY (tozinameran) 10 micrograms; 725 placebo] children have been followed for at least ≥4 months after the second dose in the placebo-controlled blinded follow-up period. 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, chills and diarrhoea (>10%).

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

In an analysis of Study C4591007 (Phase 2/3), 3,541 children [2,368 COMIRNATY (tozinameran) 3 micrograms; 1,173 placebo] were 2 to <5 years age. Based on data in the blinded placebo-controlled follow-up period up to the cutoff date of 28 February 2023, 1,268 children 2 to <5 years of age who received a 3-dose primary course [863 COMIRNATY (tozinameran) 3 micrograms; 405 placebo] have been followed a median of 2.2 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), 2,176 infants [1,458 COMIRNATY (tozinameran) 3 micrograms; 718 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 28 February 2023, 720 infants 6 months to <2 years of age who received a 3-dose primary course [483 COMIRNATY (tozinameran) 3 micrograms; 237 placebo] have been followed for a median of 1.7 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 12 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 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 (tozinameran); 386 placebo] have been followed for ≥ 4 months after the booster dose of COMIRNATY (tozinameran). The overall safety profile for the booster dose was similar to that seen after 2 doses.

In another subset from Study C4591001, 825 adolescents 12 to 15 years of age who completed the COMIRNATY (tozinameran) 2-dose course, received a booster dose of COMIRNATY (tozinameran) approximately 11.2 months (range of 6.3 to 20.1 months) after receiving Dose 2. Overall, participants who received a booster dose, had a median follow-up time of 9.5 months (range 1.5 to 10.7 months) based on data up to the cut-off date (3 November 2022). No new adverse reactions of COMIRNATY (tozinameran) were identified.

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

In a subset from study C4591031 (Phase 3), 325 adults 18 to ≤55 years of age who had completed 3 doses of COMIRNATY (tozinameran) 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 2,408 children 5 to <12 years of age received a booster dose of COMIRNATY (tozinameran) 10 micrograms at least 5 months (range 5.3 to 19.4 months) after completing the primary series. The analysis of the C4591007 Phase 2/3 subset is based on data up to the cut-off date of 28 February 2023 (median follow-up time of 6.4 months).

The most frequent adverse reactions in participants 5 to <12 years of age were injection site pain (>60%), fatigue (>30%), headache (>20%), 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. 0.7%).

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 (tozinameran) clinical trials: 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]		

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)
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] higher frequency of lymphadenopathy (2.8% vs 0.4%) was observed in participants receiving a booster dose in Study C4591031 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 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 compared to the first dose.
[d] Facial swelling in vaccine recipients with a history of injection of dermatological fillers

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

Table 2. Adverse Reactions from COMIRNATY (tozinameran) clinical trial (C4591007): Individuals 5 to <12 Years of Age (20 May 2022 Data Cut-off Date)

System Organ Class	Very Common ≥1/10 (≥10%)	Common ≥1/100 to <1/10 (≥1% to <10%)	Uncommon ≥1/1,000 to <1/100 (≥0.1% to <1%)	Rare ≥1/10,000 to <1/1,000 (≥0.01% to <0.1%)	Very Rare <1/10,000 (<0.01%)	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]	Angioedema[b,c]		Anaphylaxis[b]
Metabolism and nutrition disorders			Decreased appetite			
Nervous system disorders	Headache					

Gastrointestinal disorders	Diarrhoea[b]	Vomiting[b]	Nausea			
Skin and subcutaneous tissue disorders				Night sweats		
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. 0.7%) 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, rash and angioedema

Table 3. Adverse Reactions from COMIRNATY (tozinameran) clinical trial (C4591007): Individuals 2 to <5 Years of Age (28 February 2023 Data Cut-off Date)

System Organ Class	Very Common ≥1/10 (≥10%)	Common ≥1/100 to <1/10 (≥1% to <10%)	Uncommon ≥1/1,000 to <1/100 (≥0.1% to <1%)	Rare ≥1/10,000 to <1/1,000 (≥0.01% to <0.1%)	Very Rare <1/10,000 (<0.01%)	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		

* CIOMS frequency categories are based on clinical trial C4591007 crude incidence and was reported to only one significant figure.
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 but are still considered adverse reactions for this age group.
b. The following events are categorised as hypersensitivity reactions: rash and urticaria

Table 4. Adverse Reactions from COMIRNATY (tozinameran) clinical trial (C4591007): Individuals 6 Months to <2 Years of Age (28 February 2023 Data Cut-off Date)

System Organ Class	Very Common ≥1/10 (≥10%)	Common ≥1/100 to <1/10 (≥1% to <10%)	Uncommon ≥1/1,000 to <1/100 (≥0.1% to <1%)	Rare ≥1/10,000 to <1/1,000 (≥0.01% to <0.1%)	Very Rare <1/10,000 (<0.01%)	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			

* CIOMS frequency categories are based on clinical trial C4591007 crude incidence and was reported to only one significant figure.
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 (arm), malaise, and asthenia but are still considered adverse reactions for this age group.
b. The following events are categorised as hypersensitivity reactions: rash and urticaria

Table 5. Adverse Reactions in Individuals 18 to 55 years old Who Received a subsequent Booster (Dose 4) of COMIRNATY (tozinameran) in Study C4591031 Substudy D (SSD)

System Organ Class	Very Common ≥1/10 (≥10%)	Common ≥1/100 to <1/10 (≥1% to <10%)	Uncommon ≥1/1,000 to <1/100 (≥0.1% to <1%)	Rare ≥1/10,000 to <1/1,000 (≥0.01% to <0.1%)	Very Rare <1/10,000 (<0.01%)	Frequency not known (cannot be estimated from the available data)
Blood and lymphatic system disorders			Lymphadenopathy			

Immune system disorders						Anaphylaxis[a]
Nervous system disorders	Headache					
Cardiac disorders					Myocarditis[a] Pericarditis[a]	
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				

* CIOMS frequency categories are based on clinical trial C4591031 SSD crude incidence and was reported to only one significant figure.

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 the safety population in Study C4591031 SSD: rash, pruritus, urticaria, angioedema, decreased appetite, lethargy, nausea, hyperhidrosis, night sweats, pain in extremity, malaise, and asthenia but are still considered adverse reactions.

Table 6. Adverse Reactions in Individuals >55 years old Who Received a subsequent Booster (Dose 4) of COMIRNATY (tozinameran) in Study C4591031 Substudy E (SSE)

System Organ Class	Very Common ≥1/10 (≥10%)	Common ≥1/100 to <1/10 (≥1% to <10%)	Uncommon ≥1/1,000 to <1/100 (≥0.1% to <1%)	Rare ≥1/10,000 to <1/1,000 (≥0.01% to <0.1%)	Very Rare <1/10,000 (<0.01%)	Frequency not known (cannot be estimated from the available data)
Blood and lymphatic system disorders			Lymphadenopathy			
Immune system disorders						Anaphylaxis[a]
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[a]			
General disorders and administration site conditions	Injection site pain; Fatigue; Chills	Pyrexia; Injection site swelling; Injection site redness				

* CIOMS frequency categories are based on clinical trial C4591031 SSE crude incidence and was reported to only one significant figure.

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 the safety population in Study C4591031 SSE: rash, pruritus, urticaria, angioedema, decreased appetite, lethargy, hyperhidrosis, night sweats, malaise and asthenia but are still considered adverse reactions.

Post-marketing experience

Although the events listed in Table 5 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 7: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)
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* Breast swelling and Mastitis

[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

Safety with concomitant vaccine administration

In Study C4591030, a Phase 3 study, participants 18 to 64 years of age who received COMIRNATY (tozinameran) coadministered with seasonal inactivated influenza vaccine (SIIV), quadrivalent followed 1 month later by placebo (n=564), were compared to participants who received an inactivated influenza vaccine with placebo followed 1 month later by COMIRNATY (tozinameran) alone (n=564). Reactogenicity events were reported more frequently by participants who received COMIRNATY (tozinameran) coadministered with SIIV, quadrivalent, compared to participants who received COMIRNATY (tozinameran) alone, but overall the reactogenicity events were mostly mild to moderate in severity. The most common adverse reactions reported in the coadministration group and after COMIRNATY (tozinameran) alone were injection site pain (86.2% and 84.4%, respectively), fatigue (64.0% and 50.8%, respectively) and headache (47.2% and 37.8%, respectively).

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. 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: Covid-19 RNA-based vaccines,

ATC code: J07BN01

Mechanism of action

The nucleoside-modified messenger RNA in COMIRNATY/COMIRNATY Omicron XBB.1.5 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. COMIRNATY elicits both neutralising antibody and cellular immune responses to the antigen, which may contribute to protection against COVID-19.

Clinical trials

The efficacy of COMIRNATY Omicron XBB.1.5 is inferred from efficacy data of the prior COMIRNATY (tozinameran) vaccines.

Efficacy

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 8.

Table 8:Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of infection prior to 7 days after Dose 2 – evaluable efficacy (7 days) population

First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection*			
Subgroup	**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 9.

Table 9: 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 or 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 10) as the COVID-19 case counts in participants without prior SARS-CoV-2 infection were the same as those in participants with or without prior SARS-CoV-2 infection in both the COMIRNATY (tozinameran) and placebo groups.

Table 10. 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 11.

Table 11: 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 12. 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 12: 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.

Prespecified hypothesis-driven efficacy analysis was performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

In the efficacy analysis of Study C4591007 in children 5 to 11 years of age without evidence of prior infection, there were 10 cases out of 2,703 participants who received the vaccine and 42 cases out of 1,348 participants who received placebo. The point estimate for efficacy is 88.2% (95% CI: 76.2, 94.7). In participants with or without evidence of prior infection there were 12 cases in the 3,018 who received vaccine and 42 cases in 1,511 participants who received placebo. The point estimate for efficacy is 85.7% (95% CI: 72.4, 93.2).

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 13.

Table 13: 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 14.

Table 14: 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 N^a=264	30 microgram/dose 16 to 25 years N^a=253		
Assay	**Time point[b]**	**n^c (%) (95% CI[d])**	**n^c (%) (95% CI[d])**	**Difference %[e] (95% CI[f])**	**Met immunobridging objective[g] (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

Effectiveness in individuals 6 months to <5 years of age is based on a comparison of efficacy against symptomatic COVID-19 comparing to placebo and immune responses in this age group to individuals 16 through 25 years of age.

Efficacy in infants and children 6 months to <5 years of age – after 3 doses

The efficacy analysis of Study C4591007 was performed across the combined population of participants 6 months to <5 years of age based on cases confirmed among 873 participants in the COMIRNATY (tozinameran) group and 381 participants in the placebo group (2:1 randomisation ratio) who received all 3 doses of study intervention during the blinded

follow-up period when the Omicron variant of SARS-CoV-2 (BA.2) was the predominant variant in circulation (data cutoff date of 17 June 2022).

The vaccine efficacy results after Dose 3 in participants 6 months to <5 years of age are presented in Table 15.

Table 15: Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 3 – Blinded Follow-Up Period – Participants Without Evidence of Infection and Participants With or Without Evidence of Infection Prior to 7 Days After Dose 3 – Phase 2/3 – 6 Months to <5 Years of Age – Evaluable Efficacy (3-Dose) Population

First COVID-19 occurrence from 7 days after Dose 3 in participants without evidence of prior SARS-CoV-2 infection*			
Subgroup	**COMIRNATY (tozinameran) 3 micrograms/Dose Nᵃ=873 Cases n1[b] Surveillance Time[c] (n2[d])**	**Placebo Nᵃ=381 Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI[e])**
6 months to <5 years[e]	13 0.124 (794)	21 0.054 (351)	73.2 (43.8, 87.6)
2 to <5 years	9 0.081 (498)	13 0.033 (204)	71.8 (28.6, 89.4)
6 months to <2 years	4 0.042 (296)	8 0.020 (147)	75.8 (9.7, 94.7)
First COVID-19 occurrence from 7 days after Dose 3 in participants with or without evidence of prior SARS-CoV-2 infection			
Subgroup	**COMIRNATY (tozinameran) 3 micrograms/Dose Nᵃ=1294 Cases n1[b] Surveillance Time[c] (n2[d])**	**Placebo Nᵃ=612 Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI[e])**
6 months to <5 years[e]	14 0.149 (981)	23 0.067 (459)	72.5 (44.3, 86.9)
2 to <5 years	10 0.100 (639)	15 0.044 (286)	70.7 (30.3, 88.2)
6 months to <2 years	4 0.048 (342)	8 0.023 (173)	76.2 (11.1, 94.8)

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

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

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

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

c. Total surveillance time in 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 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.

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.

Among participants 2 to <5 years of age, severe COVID-19 criteria (as described in the protocol, based on FDA definition and modified for children) were fulfilled for 9 cases [6 COMIRNATY (tozinameran) and 3 placebo] of which 5 of the 6 cases in the COMIRNATY (tozinameran) group fulfilled a single criterion of increased heart rate or respiratory rate and all 3 cases in the placebo group fulfilled a single criterion of increased heart rate or decreased peripheral oxygen saturation. None of the cases accrued met criteria for multisystem inflammatory syndrome in children (MIS-C).

Among participants 6 months to <2 years of age, severe COVID-19 criteria were fulfilled for 3 cases [2 COMIRNATY (tozinameran) and 1 placebo] of which 1 of the 2 cases in the COMIRNATY (tozinameran) group fulfilled a single criterion of increased heart rate (152 bpm) and 1 case in the placebo group fulfilled a single criterion of increased heart rate (172 bpm). None of the cases accrued met criteria for MIS-C.
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.

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

Immunogenicity in children 2 to <5 years of age – after 3 doses

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 16 and Table 17, respectively).

Table 16: 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)		GMR (95%CI) (2 to <5 years of age/16 to 25 years of age)[c,d]
	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	
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 17: 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.

Immunogenicity in infants 6 months to <2 years of age – after 3 doses

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 18 and Table 19, respectively).

Table 18: 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)		**GMR (95%CI) (6 months to <2 years of age/16 to 25 years of age)[c,d]**
	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**	
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 19: 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 20.

Table 20. 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)	755.7[b] (663.1, 861.2)	3.26[c] (2.77, 3.86)	Y[d]
Seroresponse rate (%) for 50% neutralising titre†	200[e]	199[f] 99.5% (97.2%, 100.0%)	190[f] 95.0% (91.0%, 97.6%)	4.5%[g] (1.0%, 7.9%[h])	Y[i]

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; NT50 = 50% 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) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative and SARS-CoV-2 not

detected by NAAT [nasal swab]) and had a negative NAAT (nasal swab) at any unscheduled visit up to 1 month after the booster dose were included in the analysis.

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

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

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

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

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

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

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

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

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

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

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

An interim efficacy analysis of Study 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 21.

Table 21: 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; diarrhoea; vomiting).

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

a. N = Number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 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 (tozinameran) 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 22.

Table 22: 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.

Concomitant vaccine administration with influenza vaccine

In Study C4591030, a Phase 3 multicentre, randomised, observer-blind study, 1,134 participants 18 to 64 years of age who had received 3 doses of COMIRNATY (tozinameran) at least 3 months prior were randomised in a 1:1 ratio to receive either COMIRNATY (tozinameran) coadministered with a SIIV, quadrivalent (Afluria Quad) followed 1 month later by placebo (Group 1, n=568) or an inactivated influenza vaccine with placebo followed 1 month later with COMIRNATY (tozinameran) (Group 2, n=566).

The immune responses to COMIRNATY (tozinameran) and SIIV were similar after COMIRNATY (tozinameran) administered concomitantly with SIIV compared with those

elicited by either vaccine administered alone. The non-inferiority criterion was achieved for both full-length S-binding immunoglobulin G (IgG) and all 4 influenza strain-specific hemagglutination inhibition (HAI) titres.

The immunogenicity results are presented in Table 23 and Table 24.

Table 23. Geometric Mean Ratio for Full-Length S-Binding IgG Levels (U/mL) at 1 Month After COMIRNATY (tozinameran) Vaccination – Evaluable Immunogenicity Population

	Vaccine Group (as Randomised)				Coadministration Group/Separate Administration Group
	Coadministration Group		Separate-Administration Group		
Assay	n[a]	GMC[b] (95% CI[b])	n[a]	GMC[b] (95% CI[b])	GMR[c] (95% CI[c])
Full-length S-binding IgG (U/mL)	499	13806.5 (12838.9, 14847.0)	413	16254.6 (15035.5, 17572.5)	0.83 (0.77, 0.89)

Abbreviations: CI = confidence interval; GMC = geometric mean concentration; GMR = geometric mean ratio; IgG = immunoglobulin G; LLOQ = lower limit of quantitation; LS Means = least squares means; S = spike protein.
Note: The baseline was defined as Visit 1 for the coadministration group and Visit 2 for the separate-administration group.

a. n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
b. GMC and the 2-sided 95% CI were calculated by exponentiating the concentrations and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
c. GMR and the corresponding 2-sided 95% CI were calculated by exponentiating the difference in LS Means and the corresponding CIs based on analysis of logarithmically transformed assay results using a linear regression model with terms of vaccine group, age group, and the corresponding baseline assay results (log scale). Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67.

Table 24. Geometric Mean Ratio for Strain-Specific HAI Titres at 1 Month After SIIV Vaccination – Evaluable SIIV Immunogenicity Population

	Vaccine Group (as Randomized)				Coadministration Group/Separate Administration Group
	Coadministration Group		Separate Administration Group		
Strain	n[a]	GMT[b] (95% CI[b])	n[a]	GMT[b] (95% CI[b])	GMR[c] (95% CI[c])
B/Austria	514	72.4 (64.2, 81.7)	491	78.3 (69.3, 88.5)	0.89 (0.77, 1.04)
B/Phuket	520	87.4 (79.7, 95.7)	496	86.3 (78.4, 94.9)	1.00 (0.89, 1.13)
H1N1 A/Victoria	516	344.3 (312.4, 379.3)	492	362.3 (326.3, 401.6)	0.95 (0.83, 1.09)
H3N2 A/Darwin	519	230.6 (209.5, 253.8)	491	242.2 (221.2, 265.2)	0.96 (0.85, 1.09)

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; HAI = hemagglutination inhibition; LLOQ = lower limit of quantitation; LS Means = least squares means; SIIV = seasonal inactivated influenza vaccine; ULOQ = upper limit of quantitation.
Note: The baseline for the SIIV assay was defined at Visit 1.

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

b. GMTs and the 2-sided 95% CIs were calculated by exponentiating the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ, and results above the ULOQ were set to ULOQ + 1.
c. GMRs and the corresponding 2-sided 95% CI were calculated by exponentiating the difference in LS Means and the corresponding CIs based on analysis of logarithmically transformed assay results using a linear regression model with terms of vaccine group, age group, and the corresponding baseline assay results (log scale). Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Genotoxicity/Carcinogenicity

Neither genotoxicity nor carcinogenicity studies were performed. The components of COMIRNATY Omicron XBB.1.5 (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 Omicron XBB.1.5 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 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.

Thawed vials can be handled in room light conditions.

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

COMIRNATY Omicron XBB.1.5 – 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 Omicron XBB.1.5 – Concentrated Suspension for injection (Orange or Maroon or Yellow 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.

COMIRNATY Omicron XBB.1.5 – Single dose Glass Prefilled Syringes, 30 micrograms, intended for refrigerated storage.

COMIRNATY glass prefilled syringes may be stored at 2°C to 8°C until the expiration date printed on the carton and syringe labels. Do not freeze.

The total time out of refrigeration (at temperatures between 8°C and 30°C) must not exceed 12 hours.

COMIRNATY Omicron XBB.1.5 – Single dose Plastic Prefilled Syringes, 30 micrograms.

COMIRNATY plastic prefilled syringes may arrive frozen at ultra-cold conditions in thermal containers with dry ice. Once received, frozen plastic prefilled syringes may be immediately transferred to the refrigerator at 2°C to 8°C, thawed and stored for up to 10 weeks. The 10-week refrigerated expiry date should be recorded on the carton at the time of transfer. Cartons

of 10 single dose plastic prefilled syringes may take up to 2 hours to thaw at this temperature. Once thawed, they should not be refrozen.

Alternatively, frozen plastic prefilled syringes may be stored in an ultra-low temperature freezer at-90°C to -60°C. Do not store prefilled syringes at -25°C to -15°C.

Cartons of COMIRNATY plastic prefilled syringes may be received at 2°C to 8°C, and they should be stored at 2°C to 8°C. Check that the carton has been previously updated to reflect the 10-week refrigerated expiry date.

The total time out of refrigeration (at temperatures between 8°C and 30°C) must not exceed 12 hours.

6.4 Special precautions for storage

Thawing and Storage of Vials

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) for appropriate dosage form.

Once thawed, the vaccine cannot be re-frozen.

Thawed vials can be handled in room light conditions.

Storage of Glass Prefilled Syringes

After removing the tip cap and attaching an appropriate needle, the glass prefilled syringe should be used immediately. If it cannot be used immediately, it must be used within 4 hours.

Thawing and Storage of Plastic Prefilled Syringes

Frozen COMIRNATY plastic prefilled syringes should be thawed in the carton, preferably at 2°C to 8°C for 2 hours. A full carton of plastic prefilled syringes may also be thawed at room temperature (up to 30°C) for 60 minutes. Plastic prefilled syringes thawed in the carton by either method may be stored in the refrigerator for 10 weeks. If individual frozen plastic prefilled syringes are thawed at room temperature outside of the carton, they can be kept at room temperature and must be used within 4 hours of thawing.

After removing the tip cap and attaching an appropriate needle, the plastic prefilled syringe should be used immediately. If it cannot be used immediately, it must be used within 4 hours.

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

For additional advice on storing COMIRNATY Omicron XBB.1.5, contact Pfizer Australia on 1800 675 229.

6.5 Nature and contents of container

COMIRNATY Omicron XBB.1.5 – 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 Omicron XBB.1.5 – Concentrated Suspension for injection (Orange or Maroon or Yellow cap): 2 mL clear multidose vial (Type I glass) with a stopper (synthetic bromobutyl rubber) and an Orange or a Maroon or a Yellow flip-off plastic cap with aluminium seal. Each vial contains 10 or 3 doses after dilution, see Section 4.2 Dose and method of administration.

- Orange or Maroon cap: 10 dose multidose vial after dilution
- Yellow cap: 3 dose multidose vial after dilution

Pack size: 10 vials, 195 vials

COMIRNATY Omicron XBB.1.5 Prefilled Glass Syringe: 1 mL clear glass syringe (Type I glass) with polypropylene rigid cap with a 1 mL plunger stopper (bromobutyl elastomer). Each prefilled glass syringe contains 1 dose.

Pack size: 10 Prefilled glass syringes

COMIRNATY Omicron XBB.1.5 Prefilled Plastic Syringe: 1 mL transparent plastic (cyclic-olefin-copolymer plastic) syringe with polycarbonate rigid cap with a 1 mL plunger stopper (bromobutyl elastomer). Each prefilled plastic syringe contains 1 dose.

Pack size: 10 Prefilled plastic syringes

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

2887554-49-4

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 419330 & 419371: 9 October 2023

AUST R 419331, 419332, 419370, 419372 & 428610: 22 December 2023

AUST R 442810 & 442811: 12 August 2024

10. DATE OF REVISION

05 June 2025

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Summary Table of Changes

Section changed	Summary of new information
4.2	Reformatting and consolidation of handling information
4.8, 5.1	C4591001, 6 months post dose 3 in 12 to 15 years safety data update + final CSR C4591007, 6 months post dose 3 in 6 months to <12 years data update C4591007, 6 months post dose 2 in 5 to <12 years data update C4591007, 6 months to <5 years, Vaccine efficacy data update
4.5, 4.8 & 5.1	Inclusion of flu vaccine coadministration (C4591030) data
6.3	Removal of unopened vial room temperature storage information to avoid confusion with opened vial.