NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Comirnaty® LP.8.1 COVID-19 mRNA vaccine, 3 micrograms/0.3 mL dose, concentrate for suspension for injection (Yellow cap), for age 6 months to 4 years

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

This is a multidose vial that must be diluted before use.

One yellow cap vial (0.48 mL) contains 3 doses of 0.3 mL after dilution, see sections 4.2 and 6.6. One dose (0.3 mL) contains 3 micrograms of SARS-CoV-2 spike protein (mRNA) LP.8.1, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

SARS-CoV-2 spike protein (mRNA) LP.8.1 is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (LP.8.1).

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Concentrate for suspension for injection.

The vaccine is clear to slightly opalescent frozen suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in infants and children aged 6 months to 4 years.

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

4.2 Dose and method of administration

Dose

Strength & Age Group	**Cap and Label Color**	**Dose Volume After Dilution**
3 micrograms per dose 6 months to 4 years	Yellow	0.3 mL

Infants and children 6 months to 4 years of age without history of completion of a COVID-19 primary course or prior SARS-CoV-2 infection

Comirnaty LP.8.1 3 micrograms/dose is administered intramuscularly after dilution as a primary course of 3 doses. It is recommended to administer the second dose 3 weeks after the first dose followed by a third dose administered at least 8 weeks after the second dose (see sections 4.4 and 5.1).

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

Infants and children 6 months to 4 years of age with history of completion of a COVID-19 primary course or prior SARS-CoV-2 infection

Comirnaty LP.8.1 3 micrograms/dose is administered intramuscularly after dilution as a single dose for infants and children 6 months to 4 years of age. For individuals who have previously been vaccinated with a COVID-19 vaccine, Comirnaty LP.8.1 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Comirnaty LP.8.1 (Yellow cap) is for infants and children 6 months to 4 years of age and cannot be used in individuals 5 years of age and older.

Severely immunocompromised aged 6 months to 4 years

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

Interchangeability

The interchangeability of Comirnaty LP.8.1 with other COVID-19 vaccines to complete the primary vaccination course has not been established. Individuals who have received 1 dose of Comirnaty LP.8.1 should continue to receive Comirnaty LP.8.1 to complete the primary vaccination course.

Individuals may not be protected until at least 7 days after their third dose of the vaccine. For further information on efficacy, see Section 5.1.

Comirnaty LP.8.1 (Yellow cap) should be used only for infants and children 6 months to 4 years of age.

Paediatric population

There are paediatric formulations available for children aged 5 to 11 years of age. For details, please refer to the data sheets for other fomulations. The safety and efficacy of the vaccine in infants aged less than 6 months have not yet been established.

Elderly population

Refer to the Data Sheet for Comirnaty LP.8.1suspension for injection (30 micrograms/0.3 mL dose) (Grey cap) for individuals 12 years of age and older.

Method of administration

Comirnaty LP.8.1 (Yellow cap) should be administered intramuscularly, **after dilution** (see section 6.6).

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

Do not inject the vaccine intravascularly, subcutaneously or intradermally.

Comirnaty LP.8.1 should not be mixed in the same syringe with any other vaccines or medicinal products.

For precautions to be taken before administering the vaccine, see Section 4.4 Special warnings and precautions for use. For instructions regarding thawing, handling and disposal of the vaccine, see section 6.6.

Yellow cap vial

After dilution, the yellow cap vials contain 3 doses of 0.3 mL of vaccine.

In order to extract 3 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 tenth 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 thawing, handling, dilution and dose preparation of the vaccine before administration see Section 6.6 Special precautions for disposal and other handling.

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 clearly recorded.

General recommendations

Hypersensitivity and anaphylaxis

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

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

Myocarditis and pericarditis

Very rare cases of myocarditis and pericarditis have been observed following vaccination with Comirnaty. These cases have primarily occurred within 14 days following vaccination, more often after the second vaccination, and more often, but not excluively in younger men. 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 11 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. The cases are generally mild and individuals tend to recover within a short time following standard treatment and rest. 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.

Stress-related responses

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.

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 LP.8.1 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

Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to the vaccine.

Clinical data on safety and immunogenicity after administration of Comirnaty (tozinameran) in immunocompromised participants are available in 37 participants 2 to 4 years old,

65 participants 5 to 11 years old, 15 participants 12 to 17 years old, and 7 participants 18 years of age and older (see Sections 4.8 Undesirable effects and 5.1 Pharmacodynamic properties).

Duration of protection

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

Limitations of vaccine effectiveness

As with any vaccine, vaccination with Comirnaty may not protect all vaccine recipients. Individuals may not be fully protected until 7 days after their primary course of 3 doses of Comirnaty.

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.

Paediatric use

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

Effects on laboratory tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

No interaction studies have been performed.

Concomitant administration of Comirnaty LP.8.1 (3 micrograms/dose) with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation

Comirnaty LP.8.1 (Yellow cap) is not intended for individuals 5 years of age and older.

For details for use in individuals 5 years of age and older, please refer to the Data Sheet for the relevant strength and presentations.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of safety profile

The safety of Comirnaty (tozinameran) was evaluated in participants 5 years of age and older in 3 clinical studies that included 24,675 participants (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 11 years of age, 2,368 participants 2 to 4 years of age and 1,458 participants 6 to 23 months of age from Study C4591007) that have received at least one dose of Comirnaty (tozinameran).

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

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

In a subset of C4591007 Phase 2/3 participants, 401 participants 5 to 11 years of age received a booster dose of Comirnaty at least 5 months after completing the primary series. The overall safety profile for the booster dose was similar to that seen after the primary series.

In a subset of Study C4591054 (Substudy A, Phase 2/3), 412 participants 12 years of age and older, who had received at least 3 doses of an mRNA COVID-19 vaccine, received a booster dose of Comirnaty Omicron XBB.1.5. In another substudy of Study C4591054 (Substudy B, Phase 2/3), 311 participants 12 years of age and older, who were COVID-19 vaccine-naïve, received 1 dose of Comirnaty Omicron XBB.1.5. The safety profile of Comirnaty Omicron XBB.1.5 was similar to the overall Comirnaty safety profile.

In a subset of C4591048 (Substudy E, Phase 2/3), 310 participants 5 to 11 years of age who were COVID-19 vaccine-naïve, received 1 dose of Comirnaty Omicron XBB.1.5. The safety profile of Comirnaty Omicron XBB.1.5 was similar to the overall Comirnaty safety profile.

Omicron-adapted Comirnaty

Participants 12 years of age and older – after a single dose in vaccine-naïve individuals

In a subset of C4591054 (Substudy B, Phase 2/3), 311 participants 12 years of age and older, who were considered to be baseline SARS-CoV-2 positive and COVID-19 vaccine-naïve, received 1 dose of Comirnaty Omicron XBB.1.5 (raxtozinameran). Participants had a median follow-up time of 6.4 months up to a data cut-off date of 23 April 2024.

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

Participants 5 to 11 years of age – after a single dose in vaccine-naïve individuals

In a subset of C4591048 (Substudy E, Phase 2/3), 310 participants 5 to 11 years of age who were COVID-19 vaccine-naïve, received 1 dose of Comirnaty Omicron XBB.1.5. Participants had a median follow-up time of 6.4 months up to a data cut-off date of 1 November 2024.

The safety profile of Comirnaty Omicron XBB.1.5 was similar to the overall Comirnaty safety profile. The most frequent adverse reactions in participants were pain at the injection site (>40%), fatigue (>10%), headache (>10%), and new or worsened muscle pain (>10%).

Participants 12 years of age and older – after a booster dose

In a subset of C4591054 (Substudy A, Phase 2/3), 412 participants 12 years of age and older, who had received at least 3 doses of an authorized mRNA COVID-19 vaccine, received a booster dose of Comirnaty Omicron XBB.1.5.The safety profile of Comirnaty Omicron XBB.1.5 was similar to the overall Comirnaty safety profile.

COMIRNATY (tozinameran)

Infants 6 to 23 months of age – after 3 doses

In an analysis of Study C4591007 (Phase 2/3), 1,776 infants (1,178 Comirnaty (tozinameran) 3 micrograms and 598 placebo) were 6 to 23 months of age. Based on data in the blinded placebo-controlled follow-up period up to the cut off date of April 29, 2022, 570 infants 6 to 23 months of age who received a 3 dose primary course [386 Comirnaty (tozinameran) 3 micrograms and 184 placebo] have been followed for a median of 1.3 months after the third dose.

The most frequent adverse reactions in infants 6 to 23 months 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%).

Children 2 to 4 years of age – after 3 doses

In an analysis of Study C4591007 (Phase 2/3), 2,750 children (1,835 Comirnaty (tozinameran) 3 micrograms and 915 placebo) were 2 to 4 years age. Based on data in the blinded placebo-controlled follow-up period up to the cut off date of April 29, 2022, 886 children 2 to 4 years of age who received a 3 dose primary course (606 Comirnaty (tozinameran) 3 micrograms and 280 placebo) have been followed a median of 1.4 months after the third dose.

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

Children 5 to 11 years of age – 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 11 years of age. Of these, 2,206 (1,481 Comirnaty (tozinameran) 10 micrograms and 725 placebo) children have been followed for >4 months after the second dose in the placebo-controlled blinded follow-up period. The safety evaluation in Study C4591007 is ongoing.

The most frequent adverse reactions in children 5 to 11 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%).

Adolescents 12 to 15 years of age – after 2 doses

In an analysis of long term safety follow-up in Study C4591001, 2,260 adolescents (1,131 Comirnaty (tozinameran) 30 micrograms; 1,129 placebo) were 12 to 15 years of age. Of these, 1,559 adolescents (786 Comirnaty (tozinameran) and 773 placebo) have been followed for ≥ 4 months after the second dose of Comirnaty (tozinameran). The safety evaluation in Study C4591001 is ongoing.

The most frequent adverse reactions in adolescents 12 to 15 years of age that received 2 doses were injection site pain (>90%), fatigue and headache (>70%), myalgia and chills (>40%), arthralgia and pyrexia (>20%).

Participants 16 years of age and older – after 2 doses

In Study C4591001, a total of 22,026 participants 16 years of age or older received at least 1 dose of Comirnaty (tozinameran) 30 micrograms and a total of 22,021 participants 16 years of age or older received placebo (including 138 and 145 adolescents 16 and 17 years of age in the Comirnaty (tozinameran) and placebo groups, respectively). A total of 20,519 participants 16 years of age or older received 2 doses of Comirnaty (tozinameran).

At the time of the analysis of Study C4591001 with a data cut-off of 13 March 2021 for the placebo-controlled blinded follow-up period up to the participants' unblinding dates, a total of 25,651 (58.2%) participants (13,031 Comirnaty (tozinameran) and 12,620 placebo) 16 years of age and older were followed up for ≥4 months after the second dose. This included a total of 15,111 (7,704 Comirnaty (tozinameran) and 7,407 placebo) participants 16 to 55 years of age and a total of 10,540 (5,327 Comirnaty (tozinameran) and 5,213 placebo) participants 56 years and older.

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

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

Study C4591001 also included 200 participants with confirmed stable human immunodeficiency virus (HIV) infection. The safety profile of the participants receiving Comirnaty (tozinameran) (n=100) in the individuals with stable HIV infection was similar to that seen in the general population.

Participants 16 years of age and older – after booster dose

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

The most frequent adverse reactions in participants 18 to 55 years of age were injection site pain (>80%), fatigue (>60%), headache (>40%), myalgia (>30%), chills and arthralgia (>20%).

In Study C4591031, a placebo-controlled booster study, participants 16 years of age and older recruited from Study C4591001 received a booster dose of Comirnaty (tozinameran) (5,081 participants), or placebo (5,044 participants) at least 6 months after the second dose of Comirnaty (tozinameran). Overall, participants who received a booster dose, had a median follow-up time of 2.8 months (range 0.3 to 7.5 months) after the booster dose in the blinded placebo-controlled follow-up period to the cut-off date (8 February 2022). Of these, 1281 participants (895 Comirnaty (tozinameran) and 386 placebo) have been followed for ≥ 4 months after the booster dose of Comirnaty (tozinameran).

Children 5 to 11 years of age – after booster dose

In a subset from C4591007, a total of 401 children 5 to 11 years of age received a booster dose of Comirnaty (tozinameran) 10 micrograms at least 5 months (range of 5 to 9 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 22 March 2022 (median follow-up time of 1.3 months).

The most frequent adverse reactions in participants 5 to 11 years of age were injection site pain (>70%), fatigue (>40%), headache (>30%), myalgia, chills, injection site redness, and swelling (>10%).

Tabulated list of adverse reactions from clinical studies and post-authorisation experience

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) and Comirnaty Omicron XBB.1.5 (raxtozinameran) 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]		

Metabolism and nutrition disorders			Decreased appetite		
Psychiatric disorders			Insomnia		
Nervous system disorders	Headache		Lethargy	Acute peripheral facial paralysis[b]	
Gastrointestinal disorders		Nausea;			
Skin and subcutaneous tissue disorders			Hyperhidrosis; Night sweats		
Musculoskeletal and connective tissue disorders	Arthralgia; Myalgia				
General disorders and administration site conditions	Injection site pain; Fatigue; Chills; Pyrexia[c]; Injection site swelling	Injection site redness	Asthenia; Malaise;		Facial swelling[d]

[a] A higher frequency of lymphadenopathy (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 (tozinameran) group. Onset was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.
[c] A higher frequency of pyrexia was observed after the second dose compared to the first dose. The preferred term pyrexia is a cluster term covering also body temperature increased..
[d] Facial swelling in vaccine recipients with a history of injection of dermatological fillers

Table 2. Adverse Reactions from Comirnaty (tozinameran) and Comirnaty Omicron XBB.1.5 (raxtozinameran) clinical trials: Individuals 5 to 11 Years of Age (C4591007 22 May 2022 Data Cut-off Date, C4591048 SSE 10 October 2024 Study Completion 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[a]
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 (1.9% 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 11 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: Individuals 2 to 4 Years of Age (29 April 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			
Immune system disorders			Rash[a,b]; Urticaria[a,b]			Anaphylaxis[a]
Metabolism and nutrition disorders			Decreased appetite			
Nervous system disorders		Headache				
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.
b. The following events are categorised as hypersensitivity reactions: rash and urticaria

Table 4. Adverse Reactions from Comirnaty (tozinameran) clinical trial: Individuals 6 Months to 23 months of Age (29 April 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			
Immune system disorders		Rash[a,b]	Urticaria[a,b];			Anaphylaxis[a]
Metabolism and nutrition disorders	Decreased appetite					
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, malaise, and asthenia.

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

Immunocompromised participants (adults and children)

In study C4591024, 37 participants 2 to 4 years old, 65 participants 5 to 11 years old, 15 participants 12 to 17 years old, and 7 participants 18 years of age and older from 5 different immunocompromised disease subsets (immunomodulatory therapy, solid organ transplant, stem cell transplant, non-small cell lung cancer (NSCLC)/chronic lymphocytic leukaemia (CLL) and haemodialysis) received at least 1 and up to 4 doses of Comirnaty (tozinameran) (Doses 1 and 2 were separated by 21 days, Doses 2 and 3 were separated by 28 days and Dose 4 was administered 3 to 6 months after Dose 3).

The safety profile in immunocompromised participants 2 years of age and older who received Comirnaty (tozinameran) was similar to that in non-immunocompromised participants in other clinical studies, with no newly identified 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 5: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)
Cardiac disorders	Myocarditis Pericarditis
Nervous system disorders	Dizziness
Gastrointestinal disorders	Diarrhoea Vomiting
Musculoskeletal and connective tissue disorders	Pain in extremity (arm)[a]
General disorders and administration site conditions	Extensive swelling of vaccinated limb
Reproductive system and breast disorders	Heavy menstrual bleeding[b]
[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. [b] Most cases appear to be non-serious and temporary in nature.	

Reporting suspected adverse effects

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions at https://pophealth.my.site.com/carmreportnz/s/.

4.9 Overdose

In clinical trials, participants who received up to 2 times the recommended dose of Comirnaty did not have an increase in reactogenicity or adverse reactions.

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

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

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

The nucleoside-modified messenger RNA in Comirnaty is formulated in lipid nanoparticles, which enable delivery of the non-replicating RNA into host cells to direct transient expression of the SARS-CoV-2 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 efficacy and immunogenicity

Omicron-adapted Comirnaty

Immunogenicity in participants 12 years and older – after a single dose in vaccine-naïve individuals

In a subset from C4591054, (Substudy B [Phase 2/3]), the evaluable immunogenicity population of 302 vaccine-naïve participants 12 years of age and older who were considered to be SARS−CoV-2 positive at baseline, received 1 dose of Comirnaty Omicron XBB.1.5, was compared with participants in Substudy A [a subset from C4591054, (Phase 2/3)], who received Comirnaty Omicron XBB.1.5 after at least 3 doses of an mRNA COVID-19 vaccine.

Neutralising titres against Omicron XBB.1.5 increased from baseline to 1 month after study vaccination and were greater in participants receiving Comirnaty Omicron XBB.1.5 as a single dose compared with participants who received Comirnaty Omicron XBB.1.5 after at least 3 doses of an mRNA COVID-19 vaccine. Noninferiority was met with respect to the geometric mean ratio (GMR) of Omicron XBB.1.5-neutralising titres, and the difference in seroresponse to the XBB.1.5 strain in Substudy B vaccine-naïve participants compared to the subset of Substudy A (Table 6 and Table 7).

Table 6. Model-Based Geometric Mean Ratio – C4591054 Substudy B and Subset of Substudy A – Evaluable Immunogenicity Population

		Vaccine Group (as Assigned)				Group Comparison
		Vaccine-Naïve Substudy B Comirnaty Omicron XBB.1.5 30 mcg		Vaccine-Experienced Substudy A Comirnaty Omicron XBB.1.5 30 mcg		Substudy B / Substudy A
Assay[e]	Sampling Time Point[a]	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])	GMR[d] (95% CI[d])
SARS-CoV-2 neutralisation assay - Omicron XBB.1.5 - NT50 (titre)[e]	1 month	299	4373.4 (3757.1, 5090.9)	296	2915.7 (2462.4, 3452.5)	1.93 (1.52, 2.44)[f]

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

a. Protocol-specified timing for blood sample collection.

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

c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
d. GMRs and the corresponding 2-sided 95% CIs were calculated by exponentiating the difference in least square means and the corresponding CIs based on a linear regression model with baseline assay results (log scale), age, and vaccine group as covariates.
e. SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (Omicron subvariant XBB.1.5).
f. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67.

Table 7. Adjusted Difference in Percentages of Participants With Seroresponse – C4591054 Substudy B and Subset of Substudy A – Evaluable Immunogenicity Population

		Vaccine Group (as Assigned)				Group Comparison	
		Vaccine-Naïve Substudy B Comirnaty Omicron XBB.1.5 30 mcg		Vaccine-Experienced Substudy A Comirnaty Omicron XBB.1.5 30 mcg		Adjusted Difference	
SARS-CoV-2 Neutralisation Assay[g]	Sampling Time Point[a]	N[b]	n[c] (%) (95% CI[d])	N[b]	n[c] (%) (95% CI[d])	Difference %[e]	(95% CI[f])
SARS-CoV-2 neutralisation assay - Omicron XBB.1.5 - NT50 (titre)[g]	1 month	298	253 (84.9) (80.3, 88.8)	295	218 (73.9) (68.5, 78.8)	7.31	(1.34, 13.28)[h]

Abbreviations: CI = confidence interval; NT50 = 50% neutralising titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
a. Protocol-specified timing for blood sample collection.
b. N = number of participants with valid and determinate assay results for the specified assay at both the pre-vaccination time point and the given sampling time point. These values are the denominators for the percentage calculations.
c. n = Number of participants with a seroresponse for the given assay at the given sampling time point.
d. Exact 2-sided CI, based on the Clopper and Pearson method.
e. Difference in proportions, expressed as a percentage.
f. 2-Sided CI, based on the Miettinen and Nurminen method stratified by baseline neutralising titre category (< median, ≥ median) and age group (< median, ≥ median). The median of baseline neutralising titres and median age was calculated based on the pooled data in 2 comparator groups.
g. SARS-CoV-2 NT50 were determined using a validated 384-well assay platform Omicron subvariant XBB.1.5).
h. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is >-10%.

Immunogenicity in participants 5 to 11 years of age – after a single dose in vaccine-naïve individuals

In a subset from C4591048 (Substudy E [Phase 2/3]), the evaluable immunogenicity population of 302 participants, who received a single 10 mcg dose of Comirnaty Omicron XBB.1.5 in COVID-19 vaccine-naïve participants 5 to 11 years of age was compared to COVID-19 vaccine-experienced participants, 12 to 82 years of age, who received a single 30 mcg dose of Comirnaty Omicron XBB.1.5 in C4591054 Substudy A. The majority of the participants were considered to be SARS-CoV-2 positive at baseline (98.9% participants in C4591048 SSE, 99.3% participants in C4591054 Substudy A).

The primary immunobridging analyses compared the geometric mean titres (using a GMR) and the seroresponse (defined as achieving at least 4-fold rise from baseline) rates in the

vaccine−naïve participants 5 to 11 years of age to COVID-19 vaccine-experienced participants 12 years of age and older. The immunobridging criteria were met for both the GMR and the seroresponse rates (Table 8 and Table 9).

Table 8. Geometric Mean Ratio – C4591048 Substudy E to C4591054 Substudy A - Participants at 1 Month After the Study Vaccination - Evaluable Immunogenicity Population

SARS-CoV-2 Neutralisation Assay	C4591048 SSE 5 to 11 Years of Age Comirnaty Omicron XBB.1.5 10 mcg		C4591054 SSA 12 Years of Age and older Comirnaty Omicron XBB.1.5 30 mcg		C4591048 SSE / C4591054 SSA
	n[a]	GMT[b] (95% CI[b])	n[a]	GMT[b] (95% CI[b])	GMR[c] (95% CI[c])
Omicron XBB.1.5 - NT50 (titre)[d]	285	5930.5 (5283.8, 6656.4)	302	4006.4 (3438.3, 4668.4)	1.81 (1.51, 2.16)[e]

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

a. n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
b. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
c. GMRs and 2-sided 95% CIs were calculated by exponentiating the difference of LS Means for the assay (C4591048, 5 to 11 years of age – C4591054, 12 years of age and older) and the corresponding CIs based on a linear regression model with baseline log-transformed neutralising titres, postbaseline infection status, and vaccine group as covariates.
d. SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (Omicron subvariant XBB.1.5).
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.[339]

Table 9. Difference in Percentages of Participants With Seroresponse Between C4591048 Substudy E and C4591054 Substudy A Participants at 1 Month After the Study Vaccination - Evaluable Immunogenicity Population[343]

SARS-CoV-2 Neutralisation Assay	C4591048 SSE 5 to 11 Years of Age Comirnaty Omicron XBB.1.5 10 mcg		C4591054 SSA 12 Years of Age and older Comirnaty Omicron XBB.1.5 30 mcg		Difference	
	N[a]	n[b] (%) (95% CI[c])	N[a]	n[b] (%) (95% CI[c])	%[d]	95% CI[e]
Omicron XBB.1.5 - NT50 (titre)[f]	285	253 (88.8) (84.5, 92.2)	300	231 (77.0) (71.8, 81.6)	8.97	(3.91, 14.02)[g]

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

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

a. N = Number of participants with valid and determinate assay results for the specified assay both before vaccination and at the given sampling time point. This value is the denominator for the percentage calculations.
b. n = Number of participants with seroresponse for the given assay at the given sampling time point.
c. Exact 2-sided 95% CI based on the Clopper and Pearson method.
d. Adjusted difference in proportions based on the Miettinen and Nurminen method stratified by baseline neutralising titre category (<median, ≥median), expressed as a percentage (C4591048, 5 to 11 years of age – C4591054, 12 years of age and older). The median of baseline neutralising titres was calculated based on the pooled data in 2 comparator groups.

e. 2-sided 95% CI, based on the Miettinen and Nurminen method for the difference in proportions stratified by baseline neutralising titre category (<median, ≥median), expressed as a percentage.
f. SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (Omicron subvariant XBB.1.5).
g. Immunobridging is declared if the lower bound of the 2-sided 95% CI for the adjusted difference in percentage of participants with seroresponse is greater than -10.0%.

Immunogenicity in participants 12 years of age and older – after a booster dose

In a subset from C4591054 (Substudy A, Phase 2/3), the evaluable immunogenicity population included 382 participants 12 years of age and older who had previously received at least 3 prior doses of an authorized mRNA COVID-19 vaccine, with the most recent dose being an Omicron BA.4/BA.5-adapted bivalent vaccine, received a booster dose of Comirnaty Omicron XBB.1.5. At baseline, 78.8% of participants were considered to be positive for prior SARS−CoV−2 infection.

Compared to participants receiving Comirnaty Original/Omicron BA.4-5 (C4591044), participants receiving Comirnaty Omicron XBB.1.5 (C4591054) had higher GMTs against Omicron XBB.1.5 (2622.3 [CI: 2246.6, 3060.9] versus 601.0 [CI: 499.5, 723.1]) and against Omicron BA.4/BA.5 (5105.1 [CI: 4483.4, 5813.0] versus 4146.0 [CI: 3512.6, 4893.5]) at 1 month after vaccination.

Seroresponse (NT50) was higher against Omicron XBB.1.5, and lower against Omicron BA.4/BA.5 among participants who received Comirnaty Omicron XBB.1.5 at 1 month after vaccination compared to the participants who Comirnaty Original/Omicron BA.4-5 (C4591044) with NT50 against Omicron XBB.1.5 of 73.9% (CI: 69.2%, 78.3%) versus 52.8% (CI: 45.6%, 59.9%), and NT50 against Omicron BA.4/BA.5 of 48.3% (CI: 43.2%, 53.4%) versus 63.0% (CI: 55.9%, 69.7%).Comirnaty (tozinameran)

Efficacy and immunogenicity in individuals 6 months to 4 years of age – 3-dose primary course

Effectiveness in individuals 6 months to 4 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 to 25 years of age.

Efficacy in participants 6 months to 4 years of age – after 3 doses

The efficacy analysis of Study C4591007 was performed across the combined population of participants 6 months to 4 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 4 years of age are presented in Table 10.

Table 10: 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 4 Years of Age – Evaluable Efficacy (3-Dose) Population

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

Immunogenicity in participants 2 to 4 years of age – after 3 doses

Immunogenicity analyses have been performed in the immunobridging subset of 143 C4591007 participants 2 to 4 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 4 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 4 years of age and up to 1 month after Dose 2 in participants 16 to 25 years of age. The prespecified immunobridging criteria were met for both the GMR and the seroresponse difference (Table 11 and Table 12, respectively).

Table 11: SARS-CoV-2 GMTs (NT50) at 1 month after vaccination course – immunobridging subset - participants 2 to 4 years of age (C4591007) 1 month after Dose 3 and participants 16 to 25 years of age (C4591001) 1 month after Dose 2 – without evidence of SARS-CoV-2 infection – evaluable immunogenicity population

	Comirnaty (tozinameran)		
	3 micrograms/dose 2 to 4 years of age (1 month after Dose 3) n[a]=143	30 micrograms/dose 16 to 25 years of age (1 month after Dose 2) n[a]=170	GMR (95%CI) (2 to 4 years of age/ 16 to 25 years of age)[c,d]
Assay	**GMT[b] (95% CI[b])**	**GMT[b] (95% CI[b])**	
SARS-CoV-2 neutralisation assay - NT50 (titre)[e]	1535.2 (1388.2, 1697.8)	1180.0 (1066.6, 1305.4)	1.30 (1.13, 1.50)

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

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

a. n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
b. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
c. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (2 to 4 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 12: Difference in percentages of participants with seroresponse at 1 month after vaccination course – immunobridging subset –participants 2 to 4 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)		
	3 micrograms/dose 2 to 4 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	Difference in seroresponse rates %[d] (95% CI[e])
Assay	n[b] (%) (95% CI[c])	n[b] (%) (95% CI[c])	(2 to 4 years of age minus 16 to 25 years of age)[f]
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 4 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.

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]).

An additional descriptive immunogenicity analysis was performed for participants 2 to 4 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 (tozinameran) 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 4 years of age (median 10.6 weeks). Among 34 participants 2 to 4 years of age without evidence of prior SARS-CoV-2 infection who received 3 doses of Comirnaty (tozinameran) 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 (tozinameran) 30 micrograms, Omicron neutralising GMTs were 164.2 at 1-month post Dose 3.

Immunogenicity in participants 6 to 23 months of age – after 3 doses

Immunogenicity analyses have been performed in the immunobridging subset of 82 C4591007 participants 6 months to 23 months 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 23 months 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 23 months 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 13 and Table 14, respectively).

Table 13: SARS-CoV-2 GMTs (NT50) at 1 month after vaccination course – immunobridging subset - participants 6 months to 23 months of age (C4591007) 1 month after Dose 3 and participants 16 to 25 years of age (C4591001) 1 month after Dose 2 – without evidence of SARS-CoV-2– evaluable immunogenicity population

	Comirnaty (tozinameran)		
	3 micrograms/dose 6 months to 23 months of age (1 month after Dose 3) n[a]=82	**30 micrograms/dose 16 to 25 years of age (1 month after Dose 2) n[a]=170**	**GMR (95%CI) (6 months to 23 months of age/16 to 25 years of age)[c,d]**
Assay	**GMT[b] (95% CI[b])**	**GMT[b] (95% CI[b])**	
SARS-CoV-2 neutralisation assay - NT50 (titre)[e]	1406.5 (1211.3, 1633.1)	1180.0 (1066.6, 1305.4)	1.19 (1.00, 1.42)

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

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

a. n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
b. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titre titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
c. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (6 months to 23 months 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 14: Difference in percentages of participants with seroresponse at 1 month after vaccination course – immunobridging subset – participants 6 months to 23 months 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 23 months 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 23 months 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.

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]).

An additional descriptive immunogenicity analysis was performed for participants 6 months to 23 months 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 (tozinameran) 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 23 months of age (median 12.9 weeks). Among 32 participants 6 months to 23 months of age without evidence of prior SARS-CoV-2 infection who received 3 doses of Comirnaty (tozinameran) 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.

Efficacy in other age groups

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 15.

Table 15: 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.

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]

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 16.

Table 16: 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 17) 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 17. 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 cutoff date of 13 March 2021.

The vaccine efficacy information in adolescents 12 to 15 years of age is presented in Table 18.

Table 18: Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2 – participants without evidence of infection and with or without evidence of infection prior to 7 days after Dose 2 – 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] = 1005 Cases n1[b] Surveillance time[c] (n2[d])	**Placebo N[a] = 978 Cases n1[b] Surveillance time[c] (n2[d])**	**Vaccine efficacy % (95% CI[e])**
Adolescents 12 to 15 years	0 0.154 (1001)	16 0.147 (972)	100.0 (75.3, 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] = 1110 Cases n1[b] Surveillance time[c] (n2[d])**	**Vaccine efficacy % (95% CI[e])**
Adolescents 12 to 15 years	0 0.170 (1109)	18 0.163 (1094)	100.0 (78.1, 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 subjects 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 subjects at risk for the endpoint.
e. Confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time. CI not adjusted for multiplicity.

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), which indicates a statistically greater response in the adolescents 12 to 15 years of age than that of participants 16 to 25 years of age.

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 updated vaccine efficacy information in adolescents 12 to 15 years of age is presented in Table 19.

Table 19: 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 11 years of age – after 2 doses

An initial descriptive 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 initial descriptive vaccine efficacy results in children 5 to 11 years of age without evidence of prior SARS-CoV-2 infection are presented in Table 20. 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 20: 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 micrograms/dose N[a]=1305 Cases n1[b] Surveillance Time[c] (n2[d])	**Placebo N[a]=663 Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI)**
Children 5 to 11 years of age	3 0.322 (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 11 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 11 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 11 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 11 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 21.

Table 21: Summary of geometric mean ratio for 50% neutralising titre – Comparison of children 5 to 11 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 11 years/ 16 to 25 years	
		10 microgram/dose 5 to 11 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 11 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 11 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 22.

Table 22: 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 11 years of age to Study C4591001 Phase 2/3 16 to 25 years of age – evaluable immunogenicity population

		Comirnaty (tozinameran)		5 to 11 years/ 16 to 25 years	
		10 microgram/dose 5 to 11 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 11 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.

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 23.

Table 23. 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] (2.76, 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(tozinameran)) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative and SARS-CoV-2 not detected by NAAT [nasal swab]) and had a negative NAAT (nasal swab) at any unscheduled visit up to 1 month after the booster dose were included in the analysis.

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

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

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

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

An interim efficacy analysis of Study C4591031, a placebo-controlled booster study, was performed in approximately 10,000 participants 16 years of age and older who were recruited from Study C4591001, evaluated confirmed COVID-19 cases accrued from at least 7 days after booster vaccination up to a data cut-off date of 8 February 2022 (a period when Delta and then Omicron was the predominant variant), which represents a median of 2.8 months (range 0.3 to 7.5 months) post-booster follow-up. Vaccine efficacy of the Comirnaty (tozinameran) booster dose after the primary series relative to the placebo booster group who only received the primary series dose was assessed. The relative vaccine efficacy information for participants 16 years of age and older is presented in Table 24.

Table 24: 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 11 years of age – after booster dose

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 a substantial increase in GMTs in individuals 5 to 11 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the booster dose. This analysis is summarised in Table 25.

Table 25: Summary of Geometric Mean Titres – NT50 – Participants Without Evidence of Infection – Phase 2/3 – Immunogenicity Set – 5 to 11 Years of Age – Evaluable Immunogenicity Population

		Comirnaty (tozinameran) 10 mcg/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)	1 month 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)
	3 months 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.

Immunogenicity in children 5 to 11 years of age on the Omicron variant (B1.1.529) – after booster dose

The neutralising GMTs against both the Omicron variant (B1.1.529) and reference strain were substantially increased after booster vaccination compared with after the 2-dose primary series. At 1-month post-Dose 2, the observed neutralising GMTs for the Omicron variant (B1.1.529) and reference strain were 27.6 and 323.8, respectively. At 1-month post-Dose 3, the observed neutralising GMTs for the Omicron variant (B1.1.529) and reference strain were 614.4 and 1702.8, respectively (see Table 26).

For the Omicron variant (B1.1.529), neutralising titres after booster vaccination (1-month post-Dose 3) increased 22-fold over those after the 2-dose primary series (1-month post-Dose 2). For the reference strain, the increase after the booster relative to the primary series was 5.3-fold.

Table 26: Summary of Geometric Mean Titres – Omicron-Neutralisation Subset – Participants Without Evidence of Infection – Phase 2/3 – Immunogenicity Set – 5 to 11 Years of Age – Evaluable Immunogenicity Population

		Comirnaty (tozinameran) 10 mcg/Dose	
		Vaccine Group (as Randomised)	
Assay	Time Point[b]	n[b]	GMT[c] (95% CI[c])
SARS-COV-2 FFRNT-B.1.1.529 strain (Omicron) - NT50 (titre)	1 month after Dose 2	29	27.6 (22.1, 34.5)
	1 month after Dose 3	17	614.4 (410.7, 919.2)
SARS-CoV-2 FFRNT-reference strain - NT50 (titre)	1 month after Dose 2	29	323.8 (267.5, 392.1)
	1 month after Dose 3	17	1702.8 (1282.6, 2260.7)

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

Note: Participants 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 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 assays 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.

Immunogenicity in immunocompromised participants (adults and children)

Study C4591024 is a Phase 2b, open-label study (n=124) that enrolled immunocompromised participants 2 to 17 years of age receiving immunomodulator therapy or who have undergone solid organ transplant (within the previous 3 months) and are on immunosuppression or who have undergone bone marrow or stem cell transplant at least 6 months prior to enrollment. Study C4591024 also enrolled immunocompromised participants 18 years of age and older treated for NSCLC or CLL, receiving hemodialysis for secondary to end-stage renal disease, or receiving immunomodulator therapy for an autoimmune inflammatory disorder. Study participants did not have a past clinical or microbiological diagnosis of COVID-19. Participants received 4 age-appropriate doses of Comirnaty (tozinameran) (3 micrograms, 10 micrograms, or 30 micrograms); the first 2 doses separated by 21 days, with the third dose occurring 28 days after the second dose, followed by a fourth dose, 3 to 6 months after Dose 3.

The immunogenicity results pre-vaccination and after 3 and 4 doses of Comirnaty (tozinameran) in immunocompromised participants 2 years of age and older are presented in Table 27.

Table 27. Summary of Geometric Mean Titres – Participants With or Without Evidence of Infection by Age Group – All-Available Immunogenicity Population

		Comirnaty (tozinameran)							
		3 micrograms Age Group: 2 to 4 Years		10 micrograms Age Group: 5 to 11 Years		30 micrograms Age Group: 12 to 17 Years		30 micrograms Age Group: ⩾18 Years	
Assay	Dose/ Sampling Time Point[b]	n[c]	GMT[c] (95% CI[d])	n[c]	GMT[c] (95% CI[d])	n[c]	GMT[c] (95% CI[d])	n[c]	GMT[c] (95% CI[d])
SARS-CoV-2 neutralisation assay – reference strain – NT50 (titre)[a]	1/Prevax	32	44.8 (42.2, 47.7)	62	44.5 (42.5, 46.5)	14	54.2 (33.7, 87.0)	6	82.2 (16.0, 422.5)
	3/1 Month	32	942.3 (537.1, 1653.4)	60	1566.5 (1019.9, 2405.9)	14	2940.6 (1175.5, 7356.0)	6	787.1 (66.5, 9321.5)
	4/Pre-Dose 4	29	487.8 (269.0, 884.9)	57	922.2 (586.7, 1449.3)	11	3284.5 (1609.8, 6701.3)	3	606.2 (5.3, 68756.0)
	4/1 Month	26	3447.0 (1851.0, 6419.2)	50	6463.4 (4319.7, 9670.9)	9	13457.1 (5270.1, 34362.4)	4	1031.3 (56.9, 18681.7)
	4/6 Months	25	1296.7 (674.2, 2494.0)	49	2382.3 (1554.3, 3651.2)	8	5776.1 (2801.4, 11909.2)	3	1605.6 (28.5, 90614.9)

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

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

Analysis of immunogenicity data at 1 month after Dose 3 (32 participants 2 to 4 years of age, 60 participants 5 to 11 years of age, 14 participants 12 to 17 years of age, and 6 participants 18 years of age and older) and 1 month after Dose 4 (26 participants 2 to 4 years of age, 50 participants 5 to 11 years of age, 9 participants 12 to 17 years of age, and 4 participants 18 years of age and older) in the all available immunogenicity population with or without evidence of prior infection demonstrated a vaccine-elicited immune response.

GMTs were observed to be substantially higher at 1 month after Dose 3 and further increased at 1 month after Dose 4 and remained high at 6 months after Dose 4 compared to levels observed before study vaccination across age groups and disease subsets.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Genotoxicity/Carcinogenicity

Neither genotoxicity nor carcinogenicity studies were performed. The components of Comirnaty (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)

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

Cholesterol

Trometamol

Trometamol hydrochloride

Sucrose

Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in Section 6.6 Special precautions for disposal and other handling.

6.3 Shelf life

Unopened vial

Frozen vial

18 months when stored at -90°C to -60°C.

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

For thawing instructions of the frozen vials, see Section 6.6 Special precautions for disposal and other handling.

Thawed vial

If the vaccine is received at 2°C to 8°C it should be stored at 2°C to 8°C. 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 18 month 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.

Check that the expiry date on the outer carton and/or vial has been updated to reflect the refrigerated expiry date and that the original expiry date has been crossed out.

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

Thawed vials can be handled in room light conditions.

Once thawed the vaccine should not be re-frozen.

Diluted medicinal product

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

6.4 Special precautions for storage

Check that the expiry date has been updated to reflect the refrigerated EXP date and that the original expiry date has been crossed out.

Store in the original package to protect from light. During storage, minimise exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.

For detailed instructions see Section 6.6 Special precautions for disposal and other handling.

Once thawed, the vaccine cannot be re-frozen.

Thawed vials can be handled in room light conditions.

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

For additional advice on storing Comirnaty LP.8.1, contact Pfizer New Zealand on 0800 736 363.

6.5 Nature and contents of container

Comirnaty LP.8.1 (Yellow cap, must dilute) 0.48 mL fill volume in 2 mL clear multidose vial (Type I glass) with a stopper (synthetic bromobutyl rubber) and a yellow flip-off plastic cap with aluminium seal. Each vial contains 3 doses of 0.3 mL after dilution, see Section 6.6 Special precautions for disposal and other handling.

Pack size: 10 vials

6.6 Special precautions for disposal and other handling

Comirnaty LP.8.1 Concentrate for suspension for injection (Yellow cap)

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)**
Yellow	2 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 LP.8.1 – Concentrate for Suspension for Injection (Yellow cap)

Preparation for administration

Comirnaty LP.8.1 Concentrate for 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 LP.8.1 Concentrate for suspension for injection have a Yellow cap and **requires 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.
    - *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:
    - *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:
    - *Yellow cap vials:* 1.1 mL of air
- Gently invert the diluted dispersion 10 times. **Do not shake.**
- Check appearance of vaccine after dilution.
    - *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.
    - *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.

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

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

Pfizer New Zealand Limited
P O Box 3998
Auckland, New Zealand

Toll Free Number: 0800 736 363

9. DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute this medicine:

30 October 2025

10. DATE OF REVISION OF THE TEXT

24 November 2025

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Summary of Updates

Section	Update
N/A	New Data sheet
4.4	Addition of Study C4591024 data (immunocompromised)
4.8	Addition of AE data from Study C4591024 Addition of data from Study C4591054 SSA & SSB Addition of data from Study C4591048 SSE
4.9	Inclusion of post-authorisation experience
5.1	Addition of Study C4591024 clinical data Addition of data from Study C4591054 SSA & SSB Addition of data from Study C4591048 SSE