

1. NAME OF THE MEDICINAL PRODUCT

COMIRNATY Original/Omicron BA.4-5 5/5 micrograms per dose Concentrate for Dispersion for Injection, COVID-19 mRNA Vaccine (nucleoside modified) is called COMIRNATY (Bivalent) (For Age 5 Years to <12 Years) (Vials with Orange Cap)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

This is a multidose vial and must be diluted before use. One vial (1.3 mL) contains 10 doses of 0.2 mL after dilution (see sections 4.2 and 6.6).

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

	COMIRNATY (Bivalent) (For Age 5 Years to <12 Years) (Vials with Orange Cap)
Age	5 through <12 years of age
Pharmaceutical form	Concentrate for dispersion for injection
Strength	5/5 micrograms/dose
Cap colour	Orange
Dilution	Requires dilution
Presentation	Tris/Sucrose

Tozinameran is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 (Original). Famtozinameran is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 (Omicron BA.4-5).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for dispersion for injection

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

COMIRNATY (Bivalent) (For Age 5 Years to <12 Years) (Vials with Orange Cap) is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 5 to <12 years of age.

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

4.2 Posology and method of administration

Posology

Booster dose in individuals 5 through <12 years of age

A booster dose of COMIRNATY (Bivalent) (For Age 5 Years to <12 Years) (Vials with Orange Cap) may be administered intramuscularly in individuals 5 years through <12 years of age who have previously received at least a primary vaccination course against COVID-19.

COMIRNATY (Bivalent) (For Age 5 Years to <12 Years) (Vials with Orange Cap) cannot be used in individuals 12 years of age and older.

For further information on efficacy, see section 5.1.

Paediatric population

The safety and efficacy of COMIRNATY (Bivalent) in children aged less than 5 years has not yet been established.

Method of administration

COMIRNATY (Bivalent) should be administered intramuscularly (see section 6.6). The preferred site is the deltoid muscle of the upper arm.

Do not inject the vaccine intravascularly, subcutaneously or intradermally.

After dilution, vials of COMIRNATY (Bivalent) (For Age 5 Years to <12 Years) (Vials with Orange Cap) contain 10 doses of 0.2 mL of vaccine.

Low dead-volume syringes and/or needles can be used to extract 10 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract 10 doses from a single vial. Irrespective of the type of syringe and needle:

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

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

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

For instructions regarding thawing, handling, dilution, dose preparation of vaccine before administration, and disposal of the vaccine, see section 6.6.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Traceability

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

General recommendations

Hypersensitivity and anaphylaxis

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

Close observation for at least 30 minutes is recommended following vaccination. Subsequent dose(s) of the vaccine should not be given to those who have experienced anaphylaxis to the earlier dose of COMIRNATY.

Myocarditis and pericarditis

Postmarketing data demonstrate increased risks of myocarditis and pericarditis, particularly within 7 days following the second dose. The observed risk is higher among males under 40 years of age than among females and older males. The observed risk is highest in males 12 through 17 years of age. Based on accumulating data, the reporting rates of myocarditis and pericarditis after primary series in children ages 5 through <12 years are lower than in ages 12 through 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. Although some cases required intensive care support, available data from short-term follow-up suggest that most individuals have had resolution of symptoms with conservative management. Information is not yet available about potential long-term sequelae. Vaccine recipients should be advised to avoid strenuous physical activity for two weeks after vaccination. They should be advised to seek medical attention promptly if they develop chest pain, shortness of breath or abnormal heartbeats.

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.

Thrombocytopenia and coagulation disorders

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

Immunocompromised individuals

The efficacy, safety and immunogenicity of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of COMIRNATY or COMIRNATY (Bivalent) may be lower in immunosuppressed individuals.

Duration of protection

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

Limitations of vaccine effectiveness

As with any vaccine, vaccination with COMIRNATY or COMIRNATY (Bivalent) may not protect all vaccine recipients. Individuals may not be fully protected until 7 days after their second dose of vaccine.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concomitant administration of COMIRNATY or COMIRNATY (Bivalent) with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is limited experience with use of COMIRNATY in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development (see section 5.3). Administration of COMIRNATY in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and foetus.

No data are available yet regarding the use of COMIRNATY (Bivalent) during pregnancy.

Breast-feeding

It is unknown whether COMIRNATY is excreted in human milk.

No data are available yet regarding the use of COMIRNATY (Bivalent) during breast-feeding.

Fertility

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

It is unknown whether COMIRNATY (Bivalent) has an impact on fertility.

4.7 Effects on ability to drive and use machines

COMIRNATY or COMIRNATY (Bivalent) has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under section 4.8 may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of safety profile

The safety of COMIRNATY (Original) was evaluated in participants 5 years of age and older in 3 clinical studies conducted in the United States, Europe, Turkey, South Africa, and South America. Study BNT162-01 (Study 1) enrolled 60 participants, 18 through 55 years of age and 36 participants,

56 through 85 years of age. Study C4591001 (Study 2) enrolled approximately 46,000 participants, 12 years of age or older. Study C4591007 (Study 3) enrolled approximately 2,300 participants 5 through <12 years of age.

The overall safety profile of COMIRNATY in adolescents 12 through 15 years of age was similar to that seen in participants 16 years of age and older.

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

In Study C4591031 (Study 4), a placebo-controlled booster study, 5,081 participants 16 years of age and older were recruited from Study 2 to receive a booster dose of COMIRNATY (Original) 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 Study 3 (Phase 2/3) participants, 401 participants 5 through <12 years of age received a booster dose of COMIRNATY (Original) at least 5 months after completing the primary series. The overall safety profile of COMIRNATY (Original) for the booster dose was similar to that seen after the primary series.

In a subset of Study 5 (Phase 2/3), 107 participants 12 through 17 years of age, 313 participants 18 through 55 years of age and 306 participants 56 years of age and older who had completed 3 doses of COMIRNATY (Original), received a booster dose of COMIRNATY (Bivalent BA.4/BA.5) after receiving Dose 3. The overall safety profile for COMIRNATY (Bivalent BA.4/BA.5) booster was similar to that of the 3 doses of COMIRNATY (Original).

In a subset of C4591048 (Study 6, Phase 3), 113 participants 5 to 11 years of age who had completed 3 doses of COMIRNATY (Original), received a booster dose of COMIRNATY (Bivalent BA.4/BA.5) after receiving Dose 3. The overall safety profile for COMIRNATY (Bivalent BA.4/BA.5) booster was similar to that of the 3 doses of COMIRNATY (Original).

COMIRNATY (Original)

Participants 16 years of age and older – after 2 doses

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

At the time of the analysis of Study 2, a total of 19,067 (9,531 COMIRNATY and 9,536 placebo) participants 16 years of age or older were evaluated for safety for at least 2 months after the second dose of COMIRNATY. This included a total of 10,727 (5,350 COMIRNATY and 5,377 placebo) participants 16 through 55 years of age and a total of 8,340 (4,181 COMIRNATY and 4,159 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%) and chills (>30%), arthralgia (>20%), pyrexia and injection site swelling (>10%) and were usually mild or moderate in intensity and resolved within a few days after vaccination. A slightly lower frequency of reactogenicity events was associated with greater age.

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

Study 2 also included 200 participants with confirmed stable human immunodeficiency virus (HIV) infection. The safety profile of the participants receiving COMIRNATY (Original) (n = 100) in the individuals with stable HIV infection was similar to that seen in the general population.

Adolescents 12 through 15 years of age – after 2 doses

In an analysis of long-term safety follow-up in Study 2, based on data up to the cut-off date of 13 March 2021, 2,260 adolescents [1,131 COMIRNATY (Original) and 1,129 placebo] were 12 through 15 years of age. Of these, 1,559 adolescents [786 COMIRNATY (Original) and 773 placebo] have been followed for ≥ 4 months after the second dose. The safety evaluation in Study 2 is ongoing.

The most frequent adverse reactions in adolescents 12 through 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%).

In adolescents 12 through 15 years of age, psychiatric-related serious adverse events were numerically higher in the vaccine group, 4 recipients (3 [0.3%] with depression and 1 [0.1%] with suicidal ideation) and none in the placebo group. The events in the vaccine group were confounded by prior medical history as all 4 participants had concurrent psychiatric illness including depression prior to vaccination. Currently available information is insufficient to determine a causal relationship with the vaccine.

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

In an analysis of Study 3 (Phase 2/3), 4,647 participants [3,109 COMIRNATY (Original) 10 micrograms; 1,538 placebo] were 5 through <12 years of age. Of these, 2,206 [1,481 COMIRNATY (Original) 10 micrograms and 725 placebo] participants have been followed for at least ≥ 4 months after the second dose in the placebo controlled blinded follow-up period. The safety evaluation in Study 3 is ongoing.

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

Participants 12 years of age and older – after booster dose

The safety of a booster dose of COMIRNATY (Original) in participants 12 years of age and older is inferred from safety data from studies of a booster dose of COMIRNATY (Original) in participants 16 years of age and older.

A subset from Study 2 (Phase 2/3) participants of 306 adults at least 18 through 55 years of age who completed the primary COMIRNATY (Original) 2-dose course, received a booster dose of COMIRNATY (Original) 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 (Original).

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

In Study 4, a placebo-controlled booster study, participants 16 years of age and older recruited from Study 2 received a booster dose of COMIRNATY (Original) (5,081 participants), or placebo (5,044 participants) at least 6 months after the second dose of COMIRNATY (Original). 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 (Original) and 386 placebo] have been followed for ≥ 4 months after the booster dose of COMIRNATY (Original).

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

In a subset from Study 3, a total of 401 children 5 through <12 years of age received a booster dose of COMIRNATY (Original) 10 mcg at least 5 months (range of 5 to 9 months) after completing the primary series. The analysis of the Study 3 (Phase 2/3) subset is based on data up to the cut-off date of 22 March 2022 (median follow-up time of 1.3 months).

The most frequent adverse reactions in participants 5 through <12 years of age were injection site pain (>70%), fatigue (>40%), headache (>30%), myalgia, chills, injection site redness and swelling (>10%).

Omicron-adapted COMIRNATY – after a booster dose of COMIRNATY (Bivalent BA.1) or monovalent Omicron BA.1 (fourth dose)

The safety of a booster dose of COMIRNATY (Bivalent BA.1) in participants 5 years of age and older is inferred from safety data from studies of a booster dose of COMIRNATY (Bivalent BA.1) in individuals greater than 55 years of age and also safety data from studies of a booster dose of monovalent Omicron BA.1 in individuals 18 to ≤ 55 years of age.

Participants greater than 55 years of age – after a booster dose of COMIRNATY (Bivalent BA.1)

In a subset from Study 4 (Phase 3), 305 adults greater than 55 years of age who had completed 3 doses of COMIRNATY (Original), received a booster (fourth dose) of COMIRNATY (Bivalent BA.1) 15/15 mcg 4.7 to 11.5 months after receiving Dose 3. Participants who received a booster (fourth dose) of COMIRNATY (Bivalent BA.1) had a median follow-up time of at least 1.7 months up to a data cut-off date of 16 May 2022.

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

Participants 18 to ≤ 55 years of age – after a booster dose of monovalent Omicron BA.1

A subset of 315 adults 18 to ≤ 55 years of age who had completed 3 doses of COMIRNATY (Original), received a booster (fourth dose) of monovalent Omicron BA.1 30 mcg 90 to 180 days after receiving Dose 3. Participants who received a booster (fourth dose) of monovalent Omicron BA.1 had a median follow-up time of 1.4 months. The most frequent adverse reactions in these participants were injection site pain (>70%), fatigue (>60%), headache (>40%), myalgia (>30%), chills (>30%) and arthralgia (>20%).

Omicron-adapted COMIRNATY – after a booster dose of COMIRNATY (Bivalent BA.4/BA.5)

Participants 12 years of age and older – after a booster dose of COMIRNATY (Bivalent BA.4/BA.5)

In a subset from Study 5 (Phase 2/3), 107 participants 12 to 17 years of age, 313 participants 18 to 55 years of age and 306 participants 56 years of age and older who had completed 3 doses of COMIRNATY (Original), received a booster of COMIRNATY (Bivalent BA.4/BA.5) 5.4 to 16.9 months after receiving Dose 3. Participants who received a booster of COMIRNATY (Bivalent BA.4/BA.5) had a median follow-up time of at least 1.5 months up to a data cut-off date of 31 October 2022.

The overall safety profile for the COMIRNATY (Bivalent BA.4/BA.5) booster was similar to that seen after 3 doses of COMIRNATY (Original). The most frequent adverse reactions in participants 12

years of age and older were injection site pain (>60%), fatigue (>50%), headache (>40%), myalgia (>20%), chills (>10%), and arthralgia (>10%).

Participants 5 through <12 years of age – after a booster dose of COMIRNATY (Bivalent BA.4/BA.5)
 In a subset from Study 6 (Phase 3), 113 participants 5 to 11 years of age who had completed 3 doses of COMIRNATY (Original), received a booster of COMIRNATY (Bivalent BA.4/BA.5) 2.6 to 8.5 months after receiving Dose 3. Participants who received a booster of COMIRNATY (Bivalent BA.4/BA.5) had a median follow-up time of at least 1.6 months up to a data cut-off date of 25 November 2022.

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

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

Table 1: Adverse reactions from COMIRNATY and COMIRNATY (Bivalent, Original/Omicron BA.4/5) clinical trials and post-authorisation experience in individuals 12 years of age and older*

System Organ Class	Very common ($\geq 1/10$)	Common ($\geq 1/100$ to $< 1/10$)	Uncommon ($\geq 1/1,000$ to $< 1/100$)	Rare ($\geq 1/10,000$ to $< 1/1,000$)	Very Rare ($< 1/10,000$)	Not known (cannot be estimated from the available data)
Blood and lymphatic system disorders		Lymphadenopathy ^a				
Immune system disorders			Hypersensitivity reactions (e.g., rash, pruritus, urticaria ^b , angioedema ^b)			Anaphylaxis
Metabolism and nutrition disorder			Decreased appetite			
Psychiatric disorders			Insomnia			
Nervous system disorders	Headache		Dizziness ^d ; Lethargy	Acute peripheral facial paralysis ^c		Paraesthesia ^d ; Hypoaesthesia ^d

System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Very Rare (<1/10,000)	Not known (cannot be estimated from the available data)
Cardiac disorders					Myocarditis ^d ; Pericarditis ^d	
Gastrointestinal disorders	Diarrhoea ^d	Nausea; Vomiting ^d				
Skin and subcutaneous tissue disorder			Hyperhidrosis; Night sweats			Erythema multiforme ^d
Musculoskeletal and connective tissue disorders	Arthralgia; Myalgia		Pain in extremity ^e			
General disorders and administration site conditions	Pyrexia ^f ; Injection site pain; Fatigue; Chills; Injection site swelling	Injection site redness	Asthenia; Malaise; Injection site pruritus			

* CIOMS frequency categories are based on clinical trial C4591001 crude incidence and was reported to only one significant figure.

- a. A higher frequency of lymphadenopathy (2.8% vs 0.4%) was observed in participants receiving a booster dose in Study 4 compared to participants receiving 2 doses.
- b. The frequency category for urticaria and angioedema was rare.
- c. Through the clinical trial safety follow-up period to 14 November 2020, acute peripheral facial paralysis (or palsy) was reported by four participants in the COMIRNATY group. Onset was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.
- d. Adverse reaction determined post-authorisation.
- e. Refers to vaccinated arm. A higher frequency of pain in extremity (1.1% vs. 0.8%) was observed in participants receiving a booster dose in Study 4 compared to participants receiving 2 doses.
- f. 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.

Table 2: Adverse reactions from COMIRNATY and COMIRNATY (Bivalent, Original/Omicron BA.4/5) clinical trials and post-authorisation experience in individuals 5 through <12 years of age (22 May 2022 data cut-off date)*

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

* CIOMS frequency categories are based on clinical trial C4591007 crude incidence and was reported to only one significant figure.

- These adverse reactions were identified in the post-authorisation period. At the time of the data cut-off date, the following reactions were not reported in participants 5 through <12 years of age in Study C4591007: angioedema, lethargy, myocarditis, pericarditis, asthenia, hyperhidrosis, and night sweats but are still considered adverse reactions for this age group.
- The following events are categorised as hypersensitivity reactions: urticaria, pruritus, rash and angioedema.
- A higher frequency of lymphadenopathy was observed in participants 5 through <12 years of age in Study 3 (2.5% vs. 0.7%) receiving a booster dose compared to participants receiving 2 doses.

Other Reporting Instructions

Vaccination providers may report all other adverse events, to the extent feasible, to Pfizer Singapore using the contact information below.

Email	Fax number	Telephone number
SGP.AEReporting@pfizer.com	8001012817 (local toll free)	+65 6403 8888

Adverse Event Reporting to HSA

Healthcare professionals are required to report any suspected serious adverse events observed with the use of COMIRNATY to HSA as soon as possible. All fatal and life-threatening events are to be reported as soon as possible, within 24 hours. Please report the adverse events to the Vigilance and Compliance Branch at Tel: 6866 1111, or report online at <https://www.hsa.gov.sg/adverse-events>.

4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vaccines, other viral vaccines, ATC code: J07BX03

Mechanism of action

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

Efficacy

Study 2 is a multicentre, multinational, Phase 1/2/3 randomised, placebo-controlled, observer-blind dose-finding, vaccine candidate selection and efficacy study in participants 12 years of age and older. Randomisation was stratified by age: 12 through 15 years of age, 16 through 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 2, based on data accrued through 14 November 2020, approximately 44,000 participants were randomised equally and were to receive 2 doses of COMIRNATY 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. In the clinical study, participants were required to observe a minimum interval of 60 days before or after receipt of

blood/plasma products or immunoglobulins within through conclusion of the study in order to receive either placebo or COMIRNATY.

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 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 through 17 years of age (66 in the COMIRNATY group and 68 in the placebo group) and 1,616 participants 75 years of age and older (804 in the COMIRNATY group and 812 in the placebo group).

Table 3: Demographics (Population for the Primary Efficacy Endpoint)^a

	COMIRNATY (N=18,242) n (%)	Placebo (N=18,379) n (%)
Sex		
Male	9318 (51.1)	9225 (50.2)
Female	8924 (48.9)	9154 (49.8)
Age (years)		
Mean (SD)	50.6 (15.70)	50.4 (15.81)
Median	52.0	52.0
Min, max	(12, 89)	(12, 91)
Age group		
≥12 through 15 years ^b	46 (0.3)	42 (0.2)
≥16 through 17 years	66 (0.4)	68 (0.4)
≥16 through 64 years	14,216 (77.9)	14,299 (77.8)
≥65 through 74 years	3176 (17.4)	3226 (17.6)
≥75 years	804 (4.4)	812 (4.4)
Race		
White	15,110 (82.8)	15,301 (83.3)
Black or African American	1617 (8.9)	1617 (8.8)
American Indian or Alaska Native	118 (0.6)	106 (0.6)
Asian	815 (4.5)	810 (4.4)
Native Hawaiian or other Pacific Islander	48 (0.3)	29 (0.2)
Other ^c	534 (2.9)	516 (2.8)
Ethnicity		
Hispanic or Latino	4886 (26.8)	4857 (26.4)
Not Hispanic or Latino	13,253 (72.7)	13,412 (73.0)
Not reported	103 (0.6)	110 (0.6)
Comorbidities^d		
Yes	8432 (46.2)	8450 (46.0)
No	9810 (53.8)	9929 (54.0)

- a. All eligible randomised participants who receive all vaccination(s) as randomised within the predefined window, have no other important protocol deviations as determined by the clinician, and have no evidence of SARS-CoV-2 infection prior to 7 days after Dose 2.
- b. 100 participants 12 through 15 years of age with limited follow-up in the randomised population received at least one dose (49 in the vaccine group and 51 in the placebo group). Some of these participants were included in the efficacy evaluation depending on the population analysed. They contributed to exposure information but with no confirmed COVID-19 cases, and did not affect efficacy conclusions.
- c. Includes multiracial and not reported.
- d. Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease
 - Chronic lung disease (e.g., emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, and cystic fibrosis) or moderate to severe asthma

- Significant cardiac disease (e.g., heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension)
- Obesity (body mass index ≥ 30 kg/m²)
- Diabetes (Type 1, Type 2 or gestational)
- Liver disease
- Human Immunodeficiency Virus (HIV) infection (not included in the efficacy evaluation)

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 and in total 2,222 person-years in the placebo group.

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

The vaccine efficacy information is presented in Table 4.

Table 4: Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Age Subgroup – Participants Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection*			
Subgroup	COMIRNATY N^a = 18,198 Cases n1^b Surveillance time^c (n2^d)	Placebo N^a = 18,325 Cases n1^b Surveillance time^c (n2^d)	Vaccine efficacy % (95% CI)^e
All participants	8 2.214 (17,411)	162 2.222 (17,511)	95.0 (90.0, 97.9)
16 through 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 through 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.

- N = Number of participants in the specified group.
- n1 = Number of participants meeting the endpoint definition.
- Total surveillance time in 1,000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- n2 = Number of participants at risk for the endpoint.
- Confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time. CI not adjusted for multiplicity.

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

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

Updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up through March 13, 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 5.

Table 5: Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Age Subgroup – Participants Without Evidence of Infection and Participants With or 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 N^a=20,998 Cases n^{1b} Surveillance Time^c (n^{2d})	Placebo N^a=21,096 Cases n^{1b} Surveillance Time^c (n^{2d})	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 through 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 through 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)
First COVID-19 occurrence from 7 days after Dose 2 in participants with or without* evidence of prior SARS-CoV-2 infection			
Subgroup	COMIRNATY N^a=22,166 Cases n^{1b} Surveillance Time^c (n^{2d})	Placebo N^a=22,320 Cases n^{1b} Surveillance Time^c (n^{2d})	Vaccine Efficacy % (95% CI^e)
All participants ^f	81 6.509 (21,642)	873 6.274 (21,689)	91.1 (88.8, 93.0)
16 through 64 years	74 5.073 (16,218)	727 4.879 (16,269)	90.2 (87.6, 92.4)
65 years and older	7 1.267 (4315)	128 1.232 (4326)	94.7 (88.7, 97.9)
65 through 74 years	6 1.021 (3450)	102 0.992 (3468)	94.3 (87.1, 98.0)
75 years and older	1 0.246 (865)	26 0.240 (858)	96.2 (77.2, 99.9)

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

- * Participants who had no evidence of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
- a. N = Number of participants in the specified group.
- b. n1 = Number of participants meeting the endpoint definition.
- c. Total surveillance time in 1,000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- d. n2 = Number of participants at risk for the endpoint.
- e. Two-sided 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 through 15 years of age: 0 in the COMIRNATY 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).

The updated subgroup analyses of vaccine efficacy by demographic characteristics are presented in Table 6 and Table 7.

Table 6: Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2 – Participants Without Evidence of Infection* Prior to 7 Days After Dose 2 by Demographic Characteristics – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period

Subgroup	COMIRNATY 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
Sex			
Male	42 3.246 (10,637)	399 3.047 (10,433)	90.1 (86.4, 93.0)
Female	35 3.001 (10,075)	451 2.956 (10,280)	92.4 (89.2, 94.7)
Ethnicity			
Hispanic or Latino	29 1.786 (5161)	241 1.711 (5120)	88.5 (83.0, 92.4)
Not Hispanic or Latino	47 4.429 (15,449)	609 4.259 (15,484)	92.6 (90.0, 94.6)
Race			
Black or African American	4 0.545 (1737)	48 0.527 (1737)	91.9 (78.0, 97.9)
White	67 5.208 (17,186)	747 5.026 (17,256)	91.3 (88.9, 93.4)
All others ^f	6 0.494 (1789)	55 0.451 (1720)	90.0 (76.9, 96.5)
Country			
Argentina	15 1.012 (2600)	108 0.986 (2586)	86.5 (76.7, 92.7)
Brazil	12 0.406 (1311)	80 0.374 (1293)	86.2 (74.5, 93.1)

Subgroup	COMIRNATY N^a=20,998 Cases n^{1b} Surveillance Time^c (n^{2d})	Placebo N^a=21,096 Cases n^{1b} Surveillance Time^c (n^{2d})	Vaccine Efficacy % (95% CI)^e
Germany	0 0.047 (236)	1 0.048 (242)	100.0 (-3874.2, 100.0)
South Africa	0 0.080 (291)	9 0.074 (276)	100.0 (53.5, 100.0)
Turkey	0 0.027 (228)	5 0.025 (222)	100.0 (-0.1, 100.0)
United States	50 4.674 (16,046)	647 4.497 (16,094)	92.6 (90.1, 94.5)

Notes: 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).

Included confirmed cases in participants 12 through 15 years of age: 0 in the COMIRNATY group; 16 in the placebo group.

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

- N = Number of participants in the specified group.
- n1 = Number of participants meeting the endpoint definition.
- Total surveillance time in 1,000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- n2 = Number of participants at risk for the endpoint.
- Two-sided confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
- All others = American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported race categories.

Table 7: Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2 – Participants With or Without* Evidence of Infection Prior to 7 Days After Dose 2 by Demographic Characteristics – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period

Subgroup	COMIRNATY N^a=22,166 Cases n^{1b} Surveillance Time^c (n^{2d})	Placebo N^a=22,320 Cases n^{1b} Surveillance Time^c (n^{2d})	Vaccine Efficacy % (95% CI)^e
Sex			
Male	44 3.376 (11,103)	411 3.181 (10,920)	89.9 (86.2, 92.8)
Female	37 3.133 (10,539)	462 3.093 (10,769)	92.1 (88.9, 94.5)
Ethnicity			
Hispanic or Latino	32 1.862 (5408)	245 1.794 (5391)	87.4 (81.8, 91.6)
Not Hispanic or Latino	48 4.615 (16,128)	628 4.445 (16,186)	92.6 (90.1, 94.6)

Subgroup	COMIRNATY N^a=22,166 Cases n1^b Surveillance Time^c (n2^d)	Placebo N^a=22,320 Cases n1^b Surveillance Time^c (n2^d)	Vaccine Efficacy % (95% CI)^e
Race			
Black or African American	4 0.611 (1958)	49 0.601 (1985)	92.0 (78.1, 97.9)
White	69 5.379 (17,801)	768 5.191 (17,880)	91.3 (88.9, 93.3)
All others ^f	8 0.519 (1883)	56 0.481 (1824)	86.8 (72.1, 94.5)
Country			
Argentina	16 1.033 (2655)	110 1.017 (2670)	85.7 (75.7, 92.1)
Brazil	14 0.441 (1419)	82 0.408 (1401)	84.2 (71.9, 91.7)
Germany	0 0.047 (237)	1 0.048 (243)	100.0 (-3868.6, 100.0)
South Africa	0 0.099 (358)	10 0.096 (358)	100.0 (56.6, 100.0)
Turkey	0 0.029 (238)	6 0.026 (232)	100.0 (22.2, 100.0)
United States	51 4.861 (16,735)	664 4.678 (16,785)	92.6 (90.2, 94.6)

Notes: 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).

Included confirmed cases in participants 12 through 15 years of age: 0 in the COMIRNATY group; 18 in the placebo group.

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

- N = Number of participants in the specified group.
- n1 = Number of participants meeting the endpoint definition.
- Total surveillance time in 1,000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- n2 = Number of participants at risk for the endpoint.
- Two-sided confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
- All others = American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported race categories.

The updated subgroup analyses of vaccine efficacy by risk status in participants are presented in Table 8 and Table 9.

Table 8: Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – Participants Without Evidence of Infection* Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period

Subgroup	COMIRNATY N^a=20,998 Cases n^{1b} Surveillance Time^c (n^{2d})	Placebo N^a=21,096 Cases n^{1b} Surveillance Time^c (n^{2d})	Vaccine Efficacy % (95% CI)^e
First COVID-19 occurrence from 7 days after Dose 2 ^f	77 6.247 (20,712)	850 6.003 (20,713)	91.3 (89.0, 93.2)
At risk ^g			
Yes	35 2.797 (9167)	401 2.681 (9136)	91.6 (88.2, 94.3)
No	42 3.450 (11,545)	449 3.322 (11,577)	91.0 (87.6, 93.6)
Age group (years) and risk status			
16 through 64 and not at risk	41 2.776 (8887)	385 2.661 (8886)	89.8 (85.9, 92.8)
16 through 64 and at risk	29 2.083 (6632)	325 1.993 (6629)	91.5 (87.5, 94.4)
65 and older and not at risk	1 0.553 (1870)	53 0.546 (1922)	98.1 (89.2, 100.0)
65 and older and at risk	6 0.680 (2322)	71 0.656 (2304)	91.8 (81.4, 97.1)
Obese ^h			
Yes	27 2.103 (6796)	314 2.050 (6875)	91.6 (87.6, 94.6)
No	50 4.143 (13,911)	536 3.952 (13,833)	91.1 (88.1, 93.5)
Age group (years) and obesity status			
16 through 64 and not obese	46 3.178 (10,212)	444 3.028 (10,166)	90.1 (86.6, 92.9)
16 through 64 and obese	24 1.680 (5303)	266 1.624 (5344)	91.3 (86.7, 94.5)
65 and older and not obese	4 0.829 (2821)	79 0.793 (2800)	95.2 (87.1, 98.7)
65 and older and obese	3 0.404 (1370)	45 0.410 (1426)	93.2 (78.9, 98.7)

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.

Subgroup	COMIRNATY N^a=20,998 Cases n^{1b} Surveillance Time^c (n^{2d})	Placebo N^a=21,096 Cases n^{1b} Surveillance Time^c (n^{2d})	Vaccine Efficacy % (95% CI)^e
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- c. Total surveillance time in 1,000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- d. n² = Number of participants at risk for the endpoint.
- e. Two-sided confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.
- f. Included confirmed cases in participants 12 through 15 years of age: 0 in the COMIRNATY group; 16 in the placebo group.
- g. At risk is defined as having at least 1 of the Charlson Comorbidity Index (CMI) category or obesity (BMI ≥ 30 kg/m² or BMI $\geq 95^{\text{th}}$ percentile [12 through 15 Years of age]).
- h. Obese is defined as BMI ≥ 30 kg/m². For 12 through 15 years age group, obesity is defined as a BMI at or above the 95th percentile. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.

Table 9: Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – Participants With or Without* Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period

Subgroup	COMIRNATY N^a=22,166 Cases n^{1b} Surveillance Time^c (n^{2d})	Placebo N^a=22,320 Cases n^{1b} Surveillance Time^c (n^{2d})	Vaccine Efficacy % (95% CI)^e
First COVID-19 occurrence from 7 days after Dose 2 ^f	81 6.509 (21,642)	873 6.274 (21,689)	91.1 (88.8, 93.0)
At risk ^g			
Yes	36 2.925 (9601)	410 2.807 (9570)	91.6 (88.1, 94.2)
No	45 3.584 (12,041)	463 3.466 (12,119)	90.6 (87.2, 93.2)
Age group (years) and risk status			
16 through 64 and not at risk	44 2.887 (9254)	397 2.779 (9289)	89.3 (85.4, 92.4)
16 through 64 and at risk	30 2.186 (6964)	330 2.100 (6980)	91.3 (87.3, 94.2)
65 and older and not at risk	1 0.566 (1920)	55 0.559 (1966)	98.2 (89.6, 100.0)
65 and older and at risk	6 0.701 (2395)	73 0.672 (2360)	92.1 (82.0, 97.2)
Obese ^h			
Yes	28 2.207 (7139)	319 2.158 (7235)	91.4 (87.4, 94.4)
No	53 4.301 (14,497)	554 4.114 (14,448)	90.8 (87.9, 93.2)

Subgroup	COMIRNATY N^a=22,166 Cases n1^b Surveillance Time^c (n2^d)	Placebo N^a=22,320 Cases n1^b Surveillance Time^c (n2^d)	Vaccine Efficacy % (95% CI)^e
Age group (years) and obesity status			
16 through 64 and not obese	49 3.303 (10,629)	458 3.158 (10,614)	89.8 (86.2, 92.5)
16 through 64 and obese	25 1.768 (5584)	269 1.719 (5649)	91.0 (86.4, 94.3)
65 and older and not obese	4 0.850 (2899)	82 0.811 (2864)	95.3 (87.6, 98.8)
65 and older and obese	3 0.417 (1415)	46 0.420 (1462)	93.4 (79.5, 98.7)

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

- * Participants who had no evidence of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
- N = Number of participants in the specified group.
 - n1 = Number of participants meeting the endpoint definition.
 - Total surveillance time in 1,000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
 - n2 = Number of participants at risk for the endpoint.
 - Two-sided confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.
 - Included confirmed cases in participants 12 through 15 years of age: 0 in the COMIRNATY group; 18 in the placebo group.
 - At risk is defined as having at least 1 of the Charlson Comorbidity Index (CMI) category or obesity (BMI ≥ 30 kg/m² or BMI $\geq 95^{\text{th}}$ percentile [12 through 15 years of age]).
 - Obese is defined as BMI ≥ 30 kg/m². For the 12 through 15 years of age group, obesity is defined as a BMI at or above the 95th percentile. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.

Efficacy against severe COVID-19 – after 2 doses

Updated efficacy analyses of secondary efficacy endpoints supported benefit of COMIRNATY in preventing severe COVID-19. Vaccine efficacy against severe COVID-19 is presented only for participants with or without prior SARS-CoV-2 infection (Table 10) as the COVID-19 case counts in participants without prior SARS-CoV-2 infection were the same as those in participants with or without prior SARS-CoV-2 infection in both the COMIRNATY and placebo groups.

Table 10: Vaccine Efficacy – First Severe COVID-19 Occurrence in Participants With or Without* Prior SARS-CoV-2 Infection Based on FDA[†] or Centers for Disease Control and Prevention (CDC)[‡] Definition After Dose 1 or From 7 Days After Dose 2 in the Placebo-Controlled Follow-up

Vaccine Efficacy – First Severe COVID-19 Occurrence Based on FDA Definition			
	COMIRNATY 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 ^c (22,505)	30 8.288 ^c (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)
Vaccine Efficacy – First Severe COVID-19 Occurrence Based on CDC Definition			
	COMIRNATY 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 8.427 ^c (22,473)	45 8.269 ^c (22,394)	97.8 (87.2, 99.9)
7 days after Dose 2 ^f	0 6.514 ^g (21,620)	32 6.391 ^g (21,693)	100 (88.0, 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.

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

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

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

- Hospitalisation;
- Admission to the Intensive Care Unit;
- Intubation or mechanical ventilation;
- Death.

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

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

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

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

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

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

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

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

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

An updated efficacy analysis of Study 2 has been performed in approximately 2,260 adolescents 12 through 15 years of age evaluating confirmed COVID-19 cases accrued up to a data cut-off date of September 2, 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 through 15 years of age is presented in Table 11.

Table 11: Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2: Without Evidence of Infection and With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-up Period, Adolescents 12 Through 15 Years of Age Evaluable Efficacy (7 Days) Population

First COVID-19 occurrence from 7 days after Dose 2 in adolescents 12 through 15 years of age without evidence of prior SARS-CoV-2 infection*			
	COMIRNATY N^a=1057 Cases n^{1b} Surveillance Time^c (n^{2d})	Placebo N^a=1030 Cases n^{1b} Surveillance Time^c (n^{2d})	Vaccine Efficacy % (95% CI^e)
Adolescents 12 through 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 through 15 years of age with or without evidence of prior SARS-CoV-2 infection			

	COMIRNATY 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 through 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.

- N = Number of participants in the specified group.
- n1 = Number of participants meeting the endpoint definition.
- Total surveillance time in 1,000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- n2 = Number of participants at risk for the endpoint.
- Two-sided confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.

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

An initial descriptive efficacy analysis of Study 3 has been performed in 1,968 children 5 through <12 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 October 8, 2021.

Table 12 presents the specific demographic characteristics in participants who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose.

Table 12: Demographics Characteristics – Participants Without Evidence of Infection Prior to 7 Days After Dose 2 – Phase 2/3 – 5 Through <12 Years of Age – Evaluable Efficacy Population

	COMIRNATY 10 micrograms/dose (N^a=1305) n^b (%)	Placebo (N^a=663) n^b (%)
Sex		
Male	679 (52.0)	343 (51.7)
Female	626 (48.0)	320 (48.3)
Age at Vaccination		
Mean (SD)	8.2 (1.93)	8.1 (1.98)
Median	8.0	8.0
Min, max	(5, 11)	(5, 11)
Race		
White	1018 (78.0)	514 (77.5)
Black or African American	76 (5.8)	48 (7.2)
American Indian or Alaska Native	<1.0%	<1.0%
Asian	86 (6.6)	46 (6.9)
Native Hawaiian or other Pacific Islander	<1.0%	<1.0%

	COMIRNATY 10 micrograms/dose (N^a=1305) n^b (%)	Placebo (N^a=663) n^b (%)
Other ^c	110 (8.4)	52 (7.8)
Ethnicity		
Hispanic or Latino	243 (18.6)	130 (19.6)
Not Hispanic or Latino	1059 (81.1)	533 (80.4)
Not reported	<1.0%	<1.0%
Comorbidities^d		
Yes	262 (20.1)	133 (20.1)
No	1043 (79.9)	530 (79.9)

- N = Number of participants in the specified group from the evaluable efficacy population with no evidence of SARS CoV-2 infection prior to 7 days after Dose 2. This value is the denominator for the percentage calculations. Evaluable efficacy population included all eligible randomised participants who received all vaccination(s) as randomised within the predefined window, had no other important protocol deviations as determined by the clinician.
- n = Number of participants with the specified characteristic.
- Includes multiracial and not reported.
- Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as participants who had at least 1 of the prespecified comorbidities based on MMWR 69(32);1081-1088 and/or obesity (BMI \geq 95th percentile).

The initial descriptive vaccine efficacy results in children 5 through <12 years of age without evidence of prior SARS-CoV-2 infection are presented in Table 13. 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 13: 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 Through <12 Years of Age Evaluable Efficacy Population

First COVID-19 Occurrence From 7 days After Dose 2 in Children 5 through <12 Years of Age Without Evidence of Prior SARS-CoV-2 Infection*			
	COMIRNATY 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 through 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.

- N = Number of participants in the specified group.
- n1 = Number of participants meeting the endpoint definition.
- Total surveillance time in 1,000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

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 3 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 through <12 years of age – after 2 doses

Study 3 is a Phase 1/2/3 study comprised of an open-label vaccine dose finding portion (Phase 1) and a multicentre, multinational, randomised, saline placebo-controlled, observer-blind efficacy portion (Phase 2/3) that has enrolled participants 5 through <12 years of age.

In Study 3, an analysis of SARS-CoV-2 50% neutralising titres (NT50) 1 month after Dose 2 in a randomly selected subset of participants demonstrated effectiveness by immunobridging of immune responses comparing children 5 through <12 years of age in the Phase 2/3 part of Study 3 to participants 16 through 25 years of age in the Phase 2/3 part of Study 2 who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2, meeting the prespecified immunobridging criteria for both the 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 through <12 years of age to that of young adults 16 through 25 years of age was 1.04 (2-sided 95% CI: 0.93, 1.18), as presented in Table 14.

Table 14: Summary of Geometric Mean Ratio for 50% Neutralising Titre – Comparison of Children 5 Through <12 Years of Age (Study 3) to Participants 16 Through 25 Years of Age (Study 2) – Participants Without* Evidence of Infection up to 1 Month After Dose 2 – Dose 2 Evaluable Immunogenicity Population

		COMIRNATY		5 Through <12 Years/ 16 Through 25 Years	
		10 micrograms /Dose 5 Through <12 Years n ^a =264	30 micrograms /Dose 16 Through 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.
- n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
 - Protocol-specified timing for blood sample collection.
 - GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
 - GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (Group 1 [5 through <12 years of age] - Group 2 [16 through 25 years of age]) and the corresponding CI (based on the Student t distribution).
 - 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 .
 - 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 through <12 years of age and 99.2% of participants 16 through 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 15.

Table 15: 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 Through <12 Years of Age to Study 2 Phase 2/3 16 Through 25 Years of Age – Evaluable Immunogenicity Population

		COMIRNATY			
		Study 3 10 micrograms /Dose 5 Through <12 Years N ^a =264	Study 2 30 micrograms /Dose 16 Through 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 $\geq 4 \times$ LLOQ is considered a seroresponse.

* 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.

- 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.
- Protocol-specified timing for blood sample collection.
- 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 through <12 years of age] – Group 2 [16 through 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 was demonstrated by evaluating non-inferiority immune responses of SARS-CoV-2 NT50 1 month after a booster dose. In Study 2, an analysis of SARS-CoV-2 NT50 demonstrated non-inferior immune responses 1 month after a booster dose compared to 1 month after Dose 2 in participants at least 18 through 55 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the booster dose, based on prespecified non-inferiority criteria for both GMR and difference in seroresponse rates. Seroresponse for a participant was defined as achieving a ≥ 4 -fold rise from baseline (before Dose 1) in NT50 (Table 16 and Table 17).

The SARS-CoV-2 NT50 GMR of 1 month after the booster dose to 1 month after Dose 2 was 3.26 (2-sided 97.5% CI: 2.76, 3.86), which met the non-inferiority criteria for GMR (lower bound of the 2-sided 97.5% CI > 0.67 and point estimate of the GMR ≥ 0.8).

A high proportion of participants (99.5%) had seroresponse 1 month after Dose 3 compared with 95.0% 1 month after Dose 2. The difference in proportions of participants with a seroresponse 1 month after the booster dose (Dose 3) and 1 month after Dose 2 (Dose 3 minus Dose 2) was 1.5% (2-sided 97.5% CI: 1.0%, 7.9%), which met the 10% non-inferiority criterion (i.e., lower bound of the 2-sided 97.5% CI $> -10\%$).

Table 16: Summary of Geometric Mean Ratio for 50% Neutralising Titre – Comparison of 1 Month After Booster Dose to 1 Month After Dose 2 – Participants Without Evidence of Infection up to 1 Month After Booster Dose* – Booster Dose Evaluable Immunogenicity Population[‡]

Assay	n ^a	COMIRNATY Sampling Time Point		1 Month After Booster Dose - 1 Month After Dose 2	Met Non-inferiority Objective ^d (Y/N)
		1 Month After Booster Dose	1 Month After Dose 2		
		GMT ^b (95% CI ^b)	GMT ^b (95% CI ^b)	GMR ^c (97.5% CI ^c)	
SARS-CoV-2 neutralisation assay - reference strain - NT50 (titre) ^c	212	2466.0 (2202.6, 2760.8)	755.7 (663.1, 861.2)	3.26 (2.76, 3.86)	Y

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.

* Participants who had no serological or virological evidence (up to 1 month after receipt of a booster dose of COMIRNATY) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative and

- SARS-CoV-2 not detected by NAAT [nasal swab]) and had a negative NAAT [nasal swab] at any unscheduled visit up to 1 month after the booster dose were included in the analysis.
- ± All eligible participants who had received 2 doses of COMIRNATY as initially randomised, with Dose 2 received within the predefined window (within 19 to 42 days after Dose 1), received a booster dose of COMIRNATY, had at least 1 valid and determinate immunogenicity result after booster dose from a blood collection within an appropriate window (within 28 to 42 days after the booster dose), and had no other important protocol deviations as determined by the clinician.
 - a. n = Number of participants with valid and determinate assay results at both sampling time points within specified window.
 - b. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
 - c. GMRs and 2-sided 97.5% CIs were calculated by exponentiating the mean differences in the logarithms of the assay and the corresponding CIs (based on the Student t distribution).
 - d. Non-inferiority 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. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralisation Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralisation is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralised.

Table 17: Percentage Difference of Participants Achieving Seroreponse – Comparison of 1 Month After Booster Dose to 1 Month After Dose 2 – Phase 3 – Participants Without Evidence of Infection up to 1 Month After Booster Dose* – Booster Dose Evaluable Immunogenicity Population[±]

Assay	N ^a	COMIRNATY Sampling Time Point		Difference (1 Month After Booster Dose - 1 Month After Dose 2)	Met Non- inferiority Objective ^f (Y/N)
		1 Month After Booster Dose	1 Month After Dose 2		
		n ^b % (95% CI) ^c	n ^b % (95% CI) ^c	% ^d (97.5% CI) ^e	
SARS-CoV-2 neutralisation assay - reference strain - NT50 (titre) ^g	200	199 99.5 (97.2, 100.0)	190 95.0 (91.0, 97.6)	4.5 (1.0, 7.9)	Y

Abbreviations: CI = confidence interval; 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.

Note: Seroreponse is defined as achieving a ≥4-fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result ≥4 × LLOQ is considered a seroreponse.

* Participants who had no serological or virological evidence (up to 1 month after receipt of booster dose) 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 booster dose were included in the analysis.

- ± All eligible participants who had received 2 doses of COMIRNATY as initially randomised, with Dose 2 received within the predefined window (within 19 to 42 days after Dose 1), received a booster dose of COMIRNATY, had at least 1 valid and determinate immunogenicity result after booster dose from a blood collection within an appropriate window (within 28 to 42 days after the booster dose), and had no other important protocol deviations as determined by the clinician.
- a. N = Number of participants with valid and determinate assay results 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.
- b. n = Number of participants with seroreponse 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 (1 month after booster dose – 1 month after Dose 2).
- e. Adjusted Wald 2-sided CI for the difference in proportions, expressed as a percentage.

- f. Non-inferiority is declared if the lower bound of the 2-sided 97.5% CI for the percentage difference is >-10%.
- 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.

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

An interim efficacy analysis of Study 4, a placebo-controlled booster study, was performed in approximately 10,000 participants 16 years of age and older who were recruited from Study 2, evaluated confirmed COVID-19 cases accrued from at least 7 days after booster vaccination up to a data cut-off date of 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 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 18.

Table 18: 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 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 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 1,000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after the booster vaccination to the end of the surveillance period.
- d. n2 = Number of participants at risk for the endpoint.
- e. Relative vaccine efficacy of the COMIRNATY booster group relative to the placebo group (non-booster).
- f. Two-sided confidence interval (CI) for relative vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.

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

Effectiveness of a booster dose of COMIRNATY 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 (Dose 3) demonstrated a substantial increase in GMTs in individuals 5 through <12 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the booster dose. This analysis is summarised in Table 19.

Table 19: Summary of Geometric Mean Titres – NT50 – Participants Without Evidence of Infection – Phase 2/3 – Immunogenicity Set – 5 Through <12 Years of Age – Evaluable Immunogenicity Population

		COMIRNATY 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 Pre-vax	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 Pre-vax	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)

		COMIRNATY 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)

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; Pre-vax = 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.

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

Immunogenicity in children 5 through <12 years of age on the Omicron variant – after booster dose

The neutralising GMTs against both the Omicron variant 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 and reference strain were 27.6 and 323.8, respectively. At 1-month post-Dose 3, the observed neutralising GMTs for the Omicron variant and reference strain were 614.4 and 1702.8, respectively (see Table 20).

For the Omicron variant, 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 20: Summary of Geometric Mean Titres – Omicron-Neutralisation Subset – Participants Without Evidence of Infection – Phase 2/3 – Immunogenicity Set – 5 Through <12 Years of Age – Evaluable Immunogenicity Population

		COMIRNATY 10 mcg/Dose	
		Vaccine Group (as Randomised)	
Assay	Time Point ^a	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.

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

Omicron-adapted COMIRNATY

The efficacy of a booster dose of COMIRNATY (Bivalent) is inferred from clinical data from the studies of a booster dose of an Omicron BA.1 adapted vaccine.

Immunogenicity in participants greater than 55 years of age – after a booster dose of COMIRNATY (Bivalent, Original/Omicron BA.1) (fourth dose)

In an analysis of a subset from Study 4 (Substudy E), 610 adults greater than 55 years of age who had completed a series of 3 doses of COMIRNATY received 1 of the following as a booster dose (fourth dose): COMIRNATY (30 mcg) or COMIRNATY (Bivalent, Original/Omicron BA.1) 15/15 mcg. GMRs and seroresponse rates were evaluated at 1 month after COMIRNATY (Bivalent, Original/Omicron BA.1) 15/15 mcg booster vaccination. COMIRNATY (Bivalent, Original/Omicron BA.1) 15/15 mcg booster dose was administered 4.7 to 11.5 months (median 6.3 months) after the third dose.

The primary objective of the analysis was to assess superiority with respect to level of neutralising titre and non-inferiority with respect to seroresponse rate of the anti-Omicron immune response induced by a dose of COMIRNATY (Bivalent, Original/Omicron BA.1) 15/15 mcg relative to the

response elicited by a dose of COMIRNATY (30 mcg) given as a fourth dose in COMIRNATY-experienced participants greater than 55 years of age.

A secondary objective was to assess non-inferiority with respect to level of neutralising titre to the Original (reference) strain induced by a dose of COMIRNATY (Bivalent, Original/Omicron BA.1) 15/15 mcg relative to the response elicited by a dose of COMIRNATY (30 mcg) given as a fourth dose.

Superiority of the anti-Omicron BA.1 neutralising titre for COMIRNATY (Bivalent, Original/Omicron BA.1) 15/15 mcg relative to COMIRNATY (30 mcg) was met, as the lower bound of the 2-sided 95% CI for GMR was >1 (Table 21).

Non-inferiority of the anti-reference strain neutralising titre for COMIRNATY (Bivalent, Original/Omicron BA.1) 15/15 mcg relative to COMIRNATY (30 mcg) was met, as the lower bound of the 2-sided 95% CI for GMR was >0.67 and the point estimate of the GMR was ≥ 0.8 .

The difference in proportions of participants who achieved seroresponse to the Omicron BA.1 variant between the Omicron BA.1 (15/15 mcg) group and COMIRNATY (30 mcg) group was 14.6 (2-sided 95% CI: 4.0, 24.9). Non-inferiority was met, as the lower limit of the 2-sided 95% CI for the difference in percentages of participants with seroresponse was >-5% (Table 22).

Table 21: Substudy E - Geometric Mean Ratios for Between Vaccine Group Comparison – Participants Without Evidence of Infection Up to 1 Month after Dose 4 – Expanded Cohort – Immunogenicity Subset – Participants Greater Than 55 Years of Age – Evaluable Immunogenicity Population

Assay	Vaccine Group (as randomised)	Sampling Time Point ^a	N ^b	GMT (95% CI) ^c	GMR (95% CI) ^d
SARS-CoV-2 neutralisation assay - Omicron BA.1 - NT50 (titre)	COMIRNATY (30 mcg)	1 month	163	455.8 (365.9, 567.6)	
	COMIRNATY (Bivalent) BA.1 (15/15 mcg)	1 month	178	711.0 (588.3, 859.2)	1.56 (1.17, 2.08)
SARS-CoV-2 neutralisation assay - reference strain - NT50 (titre)	COMIRNATY (30 mcg)	1 month	182	5998.1 (5223.6, 6887.4)	
	COMIRNATY (Bivalent) BA.1 (15/15 mcg)	1 month	186	5933.2 (5188.2, 6785.2)	0.99 (0.82, 1.20)

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

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

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

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

Table 22: Substudy E - Number (%) of Participants Achieving Seroreponse – Participants Without Evidence of Infection Up to 1 Month after Dose 4 – Expanded Cohort – Immunogenicity Subset – Participants Greater Than 55 Years of Age – Evaluable Immunogenicity Population

Assay	Vaccine Group (as randomised)	Sampling Time Point ^a	N ^b	n ^c (%) (95% CI ^d)	Difference % ^e (95% CI ^f)
SARS-CoV-2 neutralisation assay - Omicron BA.1 - NT50 (titre)	COMIRNATY (30 mcg)	1 month	149	85 (57.0) (48.7, 65.1)	
	COMIRNATY (Bivalent BA.1) (15/15 mcg)	1 month	169	121 (71.6) (64.2, 78.3)	14.6 (4.0, 24.9)

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

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

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

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

- Protocol-specified timing for blood sample collection.
- N = Number of participants with valid and determinate assay results for the specified assay at both the pre-vaccination time point and the given sampling time point. This value is the denominator for the percentage calculation.
- n = Number of participants with seroreponse at 1 month after vaccination for the given assay.
- Exact 2-sided CI based on the Clopper and Pearson method.
- Difference in proportions, expressed as a percentage (vaccine group in the corresponding row - Comirnaty [30 mcg]).
- Two-sided CI based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.

Immunogenicity in participants 18 to ≤ 55 years of age – after a booster dose of COMIRNATY or monovalent Omicron BA.1 (fourth dose)

In Substudy D [a subset from Study 2 (Phase 3) and Study 4 (Phase 3)], 640 participants 18 to ≤ 55 years of age who had completed 3 doses of COMIRNATY received 1 of the following as a booster (fourth dose): COMIRNATY (30 mcg) or monovalent Omicron BA.1 90 to 180 days after receiving Dose 3.

In the primary immunogenicity subset of participants without prior evidence of infection up to 1 month after Dose 4, the ratio of GMTs for the monovalent Omicron BA.1 group to the COMIRNATY group GMR was 1.75 (2-sided 95% CI: 1.39, 2.22) (Table 23).

The lower bound of the 2-sided 95% CI for GMR was > 1 , which meets the prespecified simple superiority criterion. Therefore, superiority of monovalent Omicron BA.1 to COMIRNATY for the Omicron variant was achieved based on the GMR at 1 month after Dose 4.

The difference in proportions of participants who achieved seroreponse between the monovalent Omicron BA.1 group and COMIRNATY group was 23.0% (2-sided 95% CI: 11.1, 34.3) (Table 24), the non-inferiority criterion (lower bound of the 2-sided 95% CI > -5) was achieved.

Table 23: Substudy D – Geometric Mean Ratios for Between Vaccine Group Comparison - Cohort 2 - Primary Immunogenicity Subset - Participants Without Evidence of Infection Up to 1 Month After Dose 4 - Evaluable Immunogenicity Population

		Vaccine Group (as randomised)				Monovalent Omicron BA.1 / COMIRNATY
		Monovalent Omicron BA.1 (30 mcg)		COMIRNATY (30 mcg)		
Assay	Dose/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 BA.1 - NT50 (titre)	1/1 month	132	1929.2 (1631.5, 2281.1)	141	1099.6 (932.0, 1297.4)	1.75 (1.39, 2.22)

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

Note: Primary immunogenicity subset = a random sample of 175 participants in each vaccine group selected from the full expanded set.

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

- Protocol-specified timing for blood sample collection.
- n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (monovalent Omicron BA.1 [30 mcg] - Comirnaty [30 mcg]) and the corresponding CI (based on the Student t distribution).

Table 24: Substudy D – Difference in Percentages of Participants With Seroresponse - Cohort 2 – Primary Immunogenicity Subset - Participants Without Evidence of Infection Up to 1 Month After Dose 4 - Evaluable Immunogenicity Population

		Vaccine Group (as randomised)				Difference
		Monovalent Omicron BA.1 (30 mcg)		COMIRNATY (30 mcg)		
Assay	Dose/Sampling Time Point ^a	N ^a	n ^b (%) (95% CI ^c)	N ^a	n ^b (%) (95% CI ^c)	% ^d (95% CI ^e)
SARS-CoV-2 neutralisation assay - Omicron BA.1 - NT50 (titre)	1/1 month	130	81 (62.3) (53.4, 70.7)	140	55 (39.3) (31.1, 47.9)	23.0 (11.1, 34.3)

		Vaccine Group (as randomised)				Difference % ^d (95% CI) ^e
		Monovalent Omicron BA.1 (30 mcg)		COMIRNATY (30 mcg)		
Assay	Dose/Sampling Time Point ^a	N ^a	n ^b (%) (95% CI) ^c	N ^a	n ^b (%) (95% CI) ^c	

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

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

Note: Primary immunogenicity subset = a random sample of 175 participants in each vaccine group selected from the full expanded set.

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

- 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. This value is the denominator for the percentage calculations.
- n = Number of participants with seroresponse for the given assay at the given sampling time point.
- Exact 2-sided CI based on the Clopper and Pearson method.
- Difference in proportions, expressed as a percentage (monovalent Omicron BA.1 [30 mcg] - Comirnaty [30 mcg]).
- 2-sided CI based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.

Immunogenicity in participants 12 years of age and older – after a booster dose of COMIRNATY (Bivalent BA.4/BA.5) (fourth dose)

In an analysis of a subset from Study 5, 105 participants 12 through 17 years of age, 297 participants 18 through 55 years of age, and 286 participants 56 years of age and older who had previously received a 2-dose primary series and 1 booster dose with COMIRNATY (Original) received COMIRNATY (Bivalent BA.4/BA.5) as a second booster dose. In participants 12 through 17 years of age, 18 through 55 years of age, and 56 years of age and older, 75.2%, 71.7% and 61.5% were positive for SARS-CoV-2 at baseline, respectively.

Analyses of NT50 against Omicron BA.4/BA.5 and against reference strain among participants 56 years of age and older who received COMIRNATY (Bivalent BA.4/BA.5) as a second booster dose in Study 5 compared to a subset of participants from Study 4 who received a second booster dose of COMIRNATY (Original) demonstrated superiority of COMIRNATY (Bivalent BA.4/BA.5) to COMIRNATY (Original) based on GMR and non-inferiority based on difference in seroresponse rates with respect to anti-Omicron BA.4/BA.5 response, and non-inferiority of anti-reference strain immune response based on GMR (Table 25 and Table 26).

Analyses of NT50 against Omicron BA.4/BA.5 among participants 18 through 55 years of age compared to participants 56 years of age and older who received COMIRNATY (Bivalent BA.4/BA.5) as a booster dose in Study 5 demonstrated non-inferiority of anti-Omicron BA.4/BA.5 response among participants 18 through 55 years of age to participants 56 years of age and older for both GMR and difference in seroresponse rates (Table 25 and Table 26).

The study also assessed the level of NT50 of the anti-Omicron BA.4/BA.5 and original SARS-CoV-2 strains pre-vaccination and 1 month after vaccination in participants who received a COMIRNATY (Bivalent BA.4/BA.5) as a second booster dose (Table 27).

Table 25: Geometric Mean Ratios – Study 5 COMIRNATY – Participants With or Without Evidence of Infection – Evaluable Immunogenicity Population

SARS-CoV-2 Neutralisation Assay	Sampling Time Point ^a	COMIRNATY (Bivalent BA.4/BA.5) Study 5				COMIRNATY (Original) Subset of Study 4		Age Group Comparison	Vaccine Group Comparison
		18 Through 55 Years of Age		56 Years of Age and Older		56 Years of Age and Older		COMIRNATY (Bivalent BA.4/BA.5) 18 Through 55 Years of Age/≥56 Years of Age	COMIRNATY (Bivalent BA.4/BA.5)/COMIRNATY (Original)
		n ^b	GMT ^c (95% CI) ^c	n ^b	GMT ^c (95% CI) ^c	n ^b	GMT ^c (95% CI) ^c	GMR ^d (95% CI) ^d	GMR ^d (95% CI) ^d
Omicron BA.4/BA.5 - NT50 (titre) ^e	1 month	297	4455.9 (3851.7, 5154.8)	284	4158.1 (3554.8, 4863.8)	282	938.9 (802.3, 1098.8)	0.98 (0.83, 1.16) ^f	2.91 (2.45, 3.44) ^g
Reference strain – NT50 (titre) ^e	1 month	-	-	286	16250.1 (14499.2, 18212.4)	289	10415.5 (9366.7, 11581.8)	-	1.38 (1.22, 1.56) ^h

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

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

Table 26: Difference in Percentages of Participants With Seroreponse – COMIRNATY (Bivalent BA.4/BA.5) from Study 5 and COMIRNATY (Original) from Subset of Study 4 – Participants With or Without Evidence of Infection – Evaluable Immunogenicity Population

SARS-CoV-2 Neutralisation Assay	Sampling Time Point ^a	COMIRNATY (Bivalent BA.4/BA.5) Study 5		COMIRNATY (Original) Subset of Study 4		Age Group Comparison	Vaccine Group Comparison ≥ 56 Years of Age		
		18 Through 55 Years of Age	56 Years of Age and Older	56 Years of Age and Older	56 Years of Age and Older				
		n ^b	N ^c (%) (95% CI ^d)	n ^b	N ^c (%) (95% CI ^d)	n ^b	N ^c (%) (95% CI ^d)	Difference ^e (95% CI ^f)	Difference ^e (95% CI ^f)
Omicron BA.4/BA.5 - NT50 (titre) ^g	1 month	294	180 (61.2) (55.4, 66.8)	282	188 (66.7) (60.8, 72.1)	273	127 (46.5) (40.5, 52.6)	-3.03 (-9.68, 3.63) ^h	26.77 (19.59, 33.95) ⁱ

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

Note: Seroreponse is defined as achieving a ≥ 4 -fold rise from baseline. If the baseline measurement is below the LLOQ, a post-vaccination assay result $\geq 4 \times$ LLOQ is considered a seroreponse.

- Protocol-specified timing for blood sample collection.
- 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. This value is the denominator for the percentage calculation.
- n = number of participants with seroreponse for the given assay at the given sampling time point.
- Exact 2-sided CI, based on the Clopper and Pearson method.
- Difference in proportions, expressed as a percentage.
- 2-sided CI based on the Miettinen and Nurminen method stratified by baseline neutralising titre category (< median, \geq median) for the difference in proportions. The median of baseline neutralising titres was calculated based on the pooled data in 2 comparator groups.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (Omicron B.1.1.529 subvariant BA.4/BA.5).
- Non-inferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroreponse is $> -10\%$.
- Non-inferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroreponse is $> -5\%$.

Table 27: Geometric Mean Titres by Baseline SARS-CoV-2 Status – COMIRNATY (Bivalent BA.4/BA.5) Groups Subset of Study 5 – Prior to and 1 Month After COMIRNATY (Bivalent BA.4/BA.5) as a Second Booster – Participants 12 Years of Age and Older – Evaluable Immunogenicity Population

SARS-CoV-2 Neutralisation Assay	Baseline SARS-CoV-2 Status	Sampling Time Point ^a	COMIRNATY (Bivalent BA.4/BA.5)					
			12 Through 17 Years of Age		18 Through 55 Years of Age		56 Years of Age and Older	
			n ^b	GMT ^c (95% CI ^c)	n ^b	GMT ^c (95% CI ^c)	n ^b	GMT ^c (95% CI ^c)
Omicron BA.4/BA.5 - NT50 (titre) ^f	All	Pre-vaccination	104	1105.8 (835.1, 1464.3)	294	569.6 (471.4, 688.2)	284	458.2 (365.2, 574.8)
		1 month	105	8212.8 (6807.3, 9908.7)	297	4455.9 (3851.7, 5154.8)	284	4158.1 (3554.8, 4863.8)
	Positive ^d	Pre-vaccination	78	1791.1 (1379.6, 2325.3)	210	1181.4 (1005.3, 1388.3)	174	1291.7 (1027.5, 1623.8)
		1 month	79	9892.5 (8114.6, 12059.8)	213	6031.6 (5203.9, 6991.0)	176	6688.9 (5664.4, 7898.8)
	Negative ^e	Pre-vaccination	26	260.2 (157.1, 430.9)	84	91.9 (71.5, 118.1)	110	88.9 (69.8, 113.4)
		1 month	26	4666.1 (3096.1, 7032.2)	84	2067.7 (1530.2, 2793.9)	108	1916.2 (1489.5, 2465.1)
Reference strain - NT50 (titre) ^f	All	Pre-vaccination	105	6863.3 (5587.8, 8430.1)	296	4017.3 (3430.7, 4704.1)	284	3690.6 (3082.2, 4419.0)
		1 month	105	23641.3 (20473.1, 27299.8)	296	16323.3 (14686.5, 18142.6)	286	16250.1 (14499.2, 18212.4)
	Positive ^d	Pre-vaccination	79	8685.4 (7062.7, 10680.9)	213	7068.6 (6251.9, 7992.0)	174	8082.1 (6843.6, 9544.8)
		1 month	79	25991.8 (22377.5, 30189.8)	212	19076.6 (17056.5, 21336.0)	176	21273.3 (18604.2, 24325.3)
	Negative ^e	Pre-vaccination	26	3356.2 (2106.9, 5346.2)	83	942.3 (705.6, 1258.3)	110	1068.0 (835.9, 1364.6)
		1 month	26	17725.2 (12376.4, 25385.7)	84	11014.6 (8793.9, 13796.0)	110	10560.6 (8827.1, 12634.5)

Abbreviations: CI = confidence interval; GMT = geometric mean titre; LLOQ = lower limit of quantitation; 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.

- Protocol-specified timing for blood sample collection.
- n = number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
- Positive N-binding antibody result at baseline, positive NAAT result at baseline, or medical history of COVID-19.
- Negative N-binding antibody result at baseline, negative NAAT result at baseline, and no medical history of COVID-19.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).

Immunogenicity in participants 5 through <12 years of age – after a booster dose of COMIRNATY (Bivalent BA.4/BA.5)

In an analysis of a subset from Study 6, 103 participants 5 through <12 years of age received COMIRNATY (Bivalent BA.4/BA.5) as a booster dose after receiving 3 prior doses of COMIRNATY (Original). Results include immunogenicity data from a comparator subset of participants 5 through <12 years of age in Study 3 who received 3 doses of COMIRNATY (Original).

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

The vaccine immunogenicity results after a booster dose in participants 5 through <12 years of age are presented in Table 28.

Table 28: Study 6 – Geometric Mean Titres, by Baseline (Dose 4 Study 6/Dose 3 Study 3) SARS-CoV-2 Status – Participants With or Without Evidence of Infection – 5 Through <12 Years of Age – Evaluable Immunogenicity Population

			Vaccine Group (as Assigned/Randomised)			
			Study 6 COMIRNATY (Bivalent BA.4/BA.5) 10 mcg Dose 4 and 1 Month After Dose 4		Study 3 COMIRNATY (Original) 10 mcg Dose 3 and 1 Month After Dose 3	
SARS-CoV-2 Neutralisation Assay	Baseline SARS-CoV-2 Status	Sampling Time Point ^a	n ^b	GMT ^c (95% CI ^c)	n ^b	GMT ^c (95% CI ^c)
Omicron BA.4/BA.5 - NT50 (titre) ^f	Overall	Pre- vaccination	102	488.3 (361.9, 658.8)	112	248.3 (187.2, 329.5)
		1 month	102	2189.9 (1742.8, 2751.7)	113	1393.6 (1175.8, 1651.7)
	Positive ^d	Pre- vaccination	58	1069.2 (782.4, 1461.1)	65	695.0 (538.4, 897.3)
		1 month	58	3465.6 (2682.8, 4476.7)	66	1893.9 (1547.6, 2317.7)
	Negative ^e	Pre- vaccination	44	173.8 (117.3, 257.4)	47	59.8 (49.0, 73.1)

			Vaccine Group (as Assigned/Randomised)			
			Study 6 COMIRNATY (Bivalent BA.4/BA.5) 10 mcg Dose 4 and 1 Month After Dose 4		Study 3 COMIRNATY (Original) 10 mcg Dose 3 and 1 Month After Dose 3	
SARS-CoV-2 Neutralisation Assay	Baseline SARS-CoV-2 Status	Sampling Time Point ^a	n ^b	GMT ^c (95% CI ^c)	n ^b	GMT ^c (95% CI ^c)
		1 month	44	1195.8 (850.2, 1681.9)	47	905.8 (703.0, 1167.2)
Reference strain - NT50 (titre) ^f	Overall	Pre- vaccination	102	2904.0 (2372.6, 3554.5)	113	1323.1 (1055.7, 1658.2)
		1 month	102	8245.9 (7108.9, 9564.9)	113	7235.1 (6331.5, 8267.8)
	Positive ^d	Pre- vaccination	58	4198.4 (3342.9, 5272.8)	66	2672.7 (2122.4, 3365.6)
		1 month	58	9228.4 (7707.0, 11050)	66	7632.5 (6471.6, 9001.5)
	Negative ^e	Pre- vaccination	44	1786.4 (1305.0, 2445.5)	47	492.9 (390.9, 621.6)
		1 month	44	7108.8 (5534.0, 9131.8)	47	6711.9 (5345.4, 8427.7)

Abbreviations: 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; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

- Protocol-specified timing for blood sample collection.
- n = number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
- For Study 6: positive N-binding antibody result at the Dose 4 visit, positive NAAT result at the Dose 4 visit, or medical history of COVID-19. For Study 3: positive N-binding antibody result at the Dose 1, 1-month post-Dose 2 (if available), or Dose 3 visit, positive NAAT result at the Dose 1, Dose 2, Dose 3, or any unscheduled illness visit up to the Dose 3 visit, or medical history of COVID-19.
- For Study 6: negative N-binding antibody result at the Dose 4 visit, negative NAAT result at the Dose 4 visit, and no medical history of COVID-19. For Study 3: negative N-binding antibody result at the Dose 1, 1-month post-Dose 2 (if available), and Dose 3 visits, negative NAAT result at the Dose 1, Dose 2, Dose 3, and any unscheduled illness visits up to the Dose 3 visit, and no medical history of COVID-19.
- SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020] and Omicron B.1.1.529 subvariant BA.4/BA.5).

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity and reproductive and developmental toxicity.

General toxicity

Rats intramuscularly administered COMIRNATY (receiving 3 full human doses once weekly, generating relatively higher levels in rats due to body weight differences) demonstrated some injection site oedema and erythema and increases in white blood cells (including basophils and eosinophils) consistent with an inflammatory response as well as vacuolation of portal hepatocytes without evidence of liver injury. All effects were reversible.

Genotoxicity/Carcinogenicity

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

Reproductive toxicity

Reproductive and developmental toxicity were investigated in rats in a combined fertility and developmental toxicity study where female rats were intramuscularly administered COMIRNATY prior to mating and during gestation (receiving 4 full human doses that generate relatively higher levels in rat due to body weight differences, spanning between pre-mating day 21 and gestational day 20). SARS-CoV-2 neutralising antibody responses were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in foetuses and offspring. There were no vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development. No COMIRNATY data are available on vaccine placental transfer or excretion in milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

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

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

Cholesterol

Tromethamine (Tris base)

Tris (hydroxymethyl) aminoethane hydrochloride (Tris HCl)

Sucrose

Water for injection

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial

18 months at -90 °C to -60 °C.

COMIRNATY (Bivalent) (For Age 5 Years to <12 Years) (Vials with Orange Cap) 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.

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; not exceeding the expiry date (EXP).

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

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

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

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

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 2 °C 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 opening precludes the risks of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

COMIRNATY (Bivalent) (For Age 5 Years to <12 Years) (Vials with Orange Cap) can be stored in a refrigerator at 2 °C to 8 °C for a single period of up to 10 weeks, not exceeding the expiry date (EXP). Alternatively, the vaccine may be stored in a freezer at -90 °C to -60 °C. The expiry date for storage at -90 °C to -60 °C is printed on the vial and outer carton after “EXP”.

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

If the vaccine is received at 2 °C to 8 °C it should be stored at 2 °C to 8 °C. Check that the expiry date has been updated to reflect the refrigerated EXP date and that the original expiry date has been crossed out.

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

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

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

Once thawed, the vaccine cannot be re-frozen.

Thawed vials can be handled in room light conditions.

6.5 Nature and contents of container

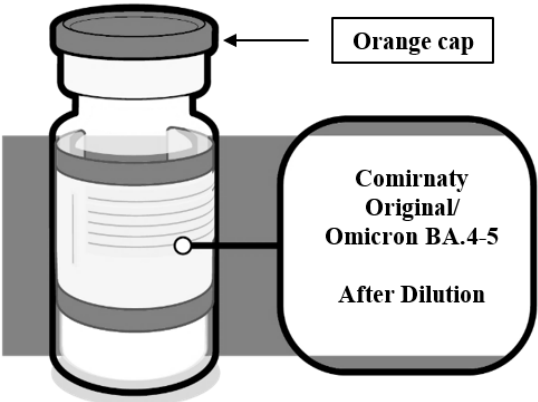
2 mL clear multidose vial (type I glass) with a stopper (synthetic bromobutyl rubber) and a flip-off plastic cap with aluminium seal, or 2 mL aluminosilicate glass vial with a stopper (bromobutyl rubber) and a flip-off plastic cap with aluminum seal.

Pack size: 10 multidose vials per carton.

6.6 Special precautions for disposal and other handling

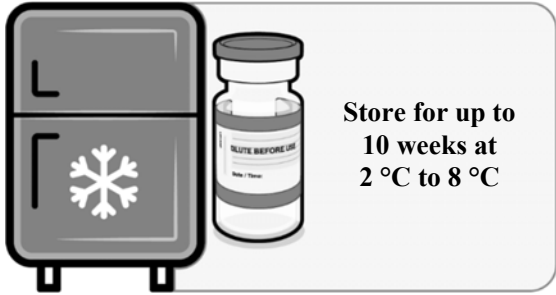
Handling instructions

COMIRNATY (Bivalent) should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.

COMIRNATY (Bivalent) (For Age 5 Years to <12 Years) (Vials with Orange Cap)	
VIAL VERIFICATION	
	<ul style="list-style-type: none"> • Verify that the vial has an orange plastic cap and an orange border around the label and the product name is COMIRNATY (Original/Omicron BA.4-5) 5/5 micrograms per dose concentrate for dispersion for injection. • If the vial has an orange plastic cap and an orange border around the label and the product name is COMIRNATY 10 micrograms/dose concentrate for dispersion for injection, refer to the handling instructions for COMIRNATY (For Age 5 Years to <12 Years) (Vials with Orange Cap). • If the vial has a grey plastic cap and a grey border around the label and the product name is COMIRNATY 30 micrograms/dose dispersion for injection, refer to the handling instructions for COMIRNATY (For 12 Years of Age and Older) (Vials with Grey Cap). • If the vial has a grey plastic cap and a grey border around the label and the product name is COMIRNATY (Original/Omicron BA.4-5) 15/15 micrograms per dose dispersion for injection, refer to the handling instructions for COMIRNATY (Bivalent) (For 12 Years of Age and Older) (Vials with Grey Cap). • If the vial has a maroon plastic cap, refer to the handling instructions for COMIRNATY (For Age 6 Months to <5 Years) (Vials with Maroon Cap).

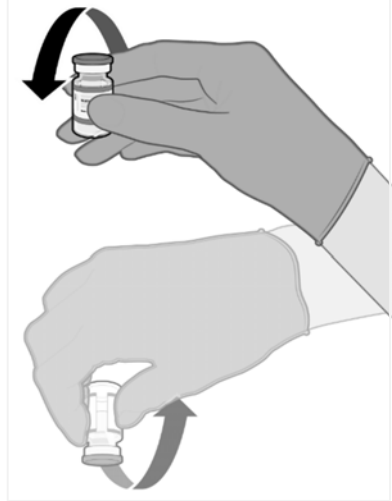
COMIRNATY (Bivalent) (For Age 5 Years to <12 Years) (Vials with Orange Cap)

HANDLING PRIOR TO USE



- If the multidose vial is stored frozen it must be thawed prior to use. Frozen vials should be transferred to an environment of 2 °C to 8 °C to thaw; a 10 vial pack may take 4 hours to thaw. Ensure vials are completely thawed prior to use.
- Unopened vials can be stored for up to 10 weeks at 2 °C to 8 °C; not exceeding the expiry date (EXP).
- Alternatively, individual frozen vials may be thawed for 30 minutes at temperatures up to 30 °C for immediate use.

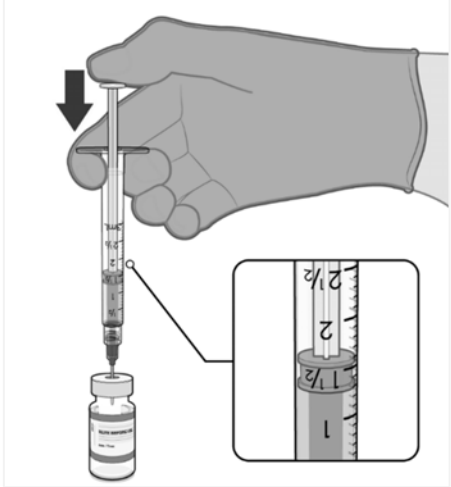
MIXING PRIOR TO DILUTION



Gently × 10

- Allow the thawed vial to come to room temperature and gently invert it 10 times prior to dilution. Do not shake.
- Prior to dilution, the thawed dispersion may contain white to off-white opaque amorphous particles.

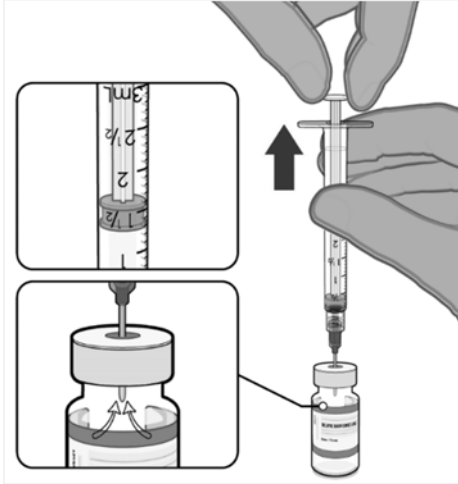
DILUTION



1.3 mL of 0.9% sodium chloride injection

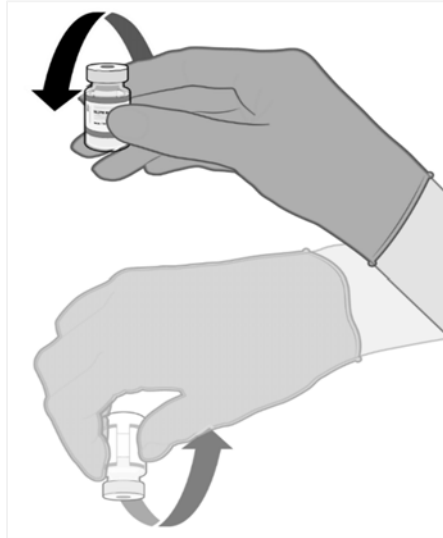
- The thawed vaccine must be diluted in its original vial with 1.3 mL sodium chloride 9 mg/mL (0.9%) solution for injection, using a 21 gauge or narrower needle and aseptic techniques.

COMIRNATY (Bivalent) (For Age 5 Years to <12 Years) (Vials with Orange Cap)



**Pull back plunger to 1.3 mL to
remove air from vial.**

- Equalize vial pressure before removing the needle from the vial stopper by withdrawing 1.3 mL air into the empty diluent syringe.



Gently × 10

- Gently invert the diluted dispersion 10 times. Do not shake.
- The diluted vaccine should present as a white to off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discoloration are present.

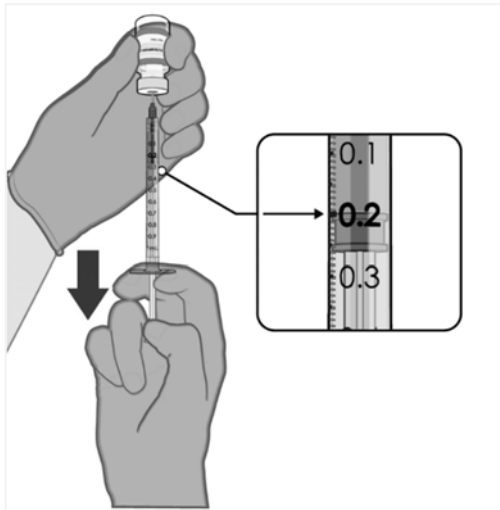
COMIRNATY (Bivalent) (For Age 5 Years to <12 Years) (Vials with Orange Cap)



**Record appropriate date and time.
Use within 12 hours after dilution.**

- The diluted vials should be marked with the appropriate date and time.
- After dilution, store at 2 °C to 30 °C and use within 12 hours.
- Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.

PREPARATION OF INDIVIDUAL 0.2 mL DOSES OF COMIRNATY (Bivalent) (For Age 5 Years to <12 Years) (Vials with Orange Cap)



0.2 mL diluted vaccine

- Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
- Withdraw 0.2 mL of COMIRNATY (Bivalent) (For Age 5 Years to <12 Years) (Vials with Orange Cap).

Low dead-volume syringes and/or needles should be used in order to extract 10 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres.

If standard syringes and needles are used, there may not be sufficient volume to extract ten doses from a single vial.

- Each dose must contain 0.2 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.2 mL, discard the vial and any excess volume.
- Discard any unused vaccine within 12 hours after dilution.

Disposal


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

7. PRODUCT OWNER

BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz
Germany

8. CONTACT INFORMATION

For general questions, visit the website or call the telephone number provided below.

Website	Telephone number
<p data-bbox="378 821 682 850">www.comirnatyglobal.com</p> 	<p data-bbox="1008 911 1175 940">+65 6403 8888</p>

For medical information enquiries, please submit your medical information enquires at <https://pmiform.com/HCP/SG>.

Alternatively, you may send them to MedicalInformationSingapore@pfizer.com.

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