1. NAME OF THE MEDICINAL PRODUCT

COMIRNATY, COVID-19 mRNA Vaccine (nucleoside-modified), 30 micrograms/dose Dispersion for Injection (Multi-dose Vial) (SIN16396P)

COMIRNATY, COVID-19 mRNA Vaccine (nucleoside-modified), 30 micrograms/dose Dispersion for Injection (Single-dose Vial) (SIN17016P)

COMIRNATY, COVID-19 mRNA Vaccine (nucleoside modified), 30 micrograms/dose Dispersion for Injection in Pre-filled Syringe (SIN17235P)

COMIRNATY, COVID-19 mRNA Vaccine (nucleoside-modified), 10 micrograms/dose Dispersion for Injection (Multi-dose Vial) (SIN16397P)

COMIRNATY, COVID-19 mRNA Vaccine (nucleoside-modified), 10 micrograms/dose Dispersion for Injection (Single-dose Vial) (SIN17017P)

COMIRNATY, COVID-19 mRNA Vaccine (nucleoside-modified), 3 micrograms/dose Concentrate for Dispersion for Injection (SIN16616P)

Name	**Refers to Vaccine Presentation(s) For This Variant**
COMIRNATY	Any presentation regardless of strain or strength.
COMIRNATY (Original)	Original monovalent vaccine encoding the viral spike (S) glycoprotein of SARS-CoV-2 Wuhan-Hu-1 strain (wildtype).
COMIRNATY (Omicron JN.1)	Monovalent Omicron-adapted vaccine encoding the viral spike (S) glycoprotein of SARS-CoV-2 Omicron variant JN.1 (may also be referred to as 2024-2025 formula).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

COMIRNATY is highly purified single-stranded, 5'-capped messenger ribonucleic acid (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2.

Each dose contains COVID-19 mRNA vaccine embedded in lipid nanoparticles.

For the full list of excipients, see section 6.1.

Table 1. Available Strengths of COMIRNATY

	Monovalent Presentations
	COMIRNATY (Omicron JN.1)
Age Range of Recipient	**Strength per dose in micrograms**
6 months to <5 years	3 micrograms of bretovameran
5 to <12 years	10 micrograms of bretovameran
12 years and older	30 micrograms of bretovameran

3. PHARMACEUTICAL FORM

Table 2. Available Presentations of COMIRNATY

Age Range of Recipient and Strength	Presentation (Vial Cap and Vial Label Colour or Pre-filled Syringe)	Pharmaceutical Form and Dilution Requirement	Presentation (Vial Fill Volume in mL and Number of Doses per Unit)	Variants for This Vaccine Presentation	Appearance
6 months to <5 years 3 micrograms/dose	Yellow	Concentrate for dispersion for injection. Must Dilute.	Multidose vial (0.48 mL) contains three 0.3 mL doses per vial after dilution	Omicron JN.1	Clear to slightly opalescent solution.
5 to <12 years 10 micrograms/dose	Dark blue	Dispersion for injection. Do not dilute.	Multidose vial (2.25 mL) contains six 0.3 mL doses per vial	Omicron JN.1	Clear to slightly opalescent solution.
	Light blue	Dispersion for injection. Do not dilute.	Single dose vial (0.48 mL) contains one 0.3 mL dose	Omicron JN.1	Clear to slightly opalescent solution.
12 years and older 30 micrograms/dose	Dark grey	Dispersion for injection. Do not dilute.	Multidose vial (2.25 mL) contains six 0.3 mL doses per vial	Omicron JN.1	White to off-white solution.
	Light grey	Dispersion for injection. Do not dilute.	Single dose vial (0.48 mL) contains one 0.3 mL dose	Omicron JN.1	White to off-white solution.
	Pre-filled syringe	Dispersion for injection. Do not dilute.	Single dose pre-filled syringe contains one 0.3 mL dose	Omicron JN.1	White to off-white solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

COMIRNATY is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 6 months of age and older.

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

4.2 Posology and method of administration

Posology

Table 3. Dosing Recommendations

Age Range of Recipient and Strength	**Presentation (Vial Cap and Vial Label Colour or Pre-filled Syringe)**	**Volume of Each Dose**	**Dose Schedule[c]**
6 months to <5 years[a] 3 micrograms/dose	Yellow	0.3 mL	**3 Dose Primary Series:** o Dose 1 and 2: 3 weeks apart o Dose 3: at least 8 weeks after second dose
5 to <12 years[a] 10 micrograms/dose	Blue[b]	0.3 mL	**2 Dose Primary Series:** o Dose 2: at least 21 days (preferably 3 weeks) after first dose
12 years and older 30 micrograms/dose	Grey[b]	0.3 mL	Single dose and in accordance with official recommendations
	Pre-filled syringe	0.3 mL	

a. Individuals who will turn from 4 years to 5 years or from 11 years to 12 years of age between their doses in the vaccination series should receive their age-appropriate dose at the time of the vaccination and the interval between doses is determined by the individual's age at the start of the vaccination series.
b. Refers to either the single dose vial presentation for the light blue and light grey caps or the multidose vial presentation for the dark blue and dark grey caps.
c. For individuals less than 12 years of age, the primary series and booster may consist of either COMIRNATY (Original), or a variant-adapted presentation of COMIRNATY, or a combination, but not exceeding the total number of doses recommended for the primary series. The primary series should only be administered once.

A booster may be administered at least 3 months after completion of primary series and in accordance with official recommendations.

Individuals who have partially completed the primary series with a COVID-19 vaccine

Individuals 6 months through <12 years of age who have partially completed the primary series should complete the primary series with an age-appropriate dose of the most current COMIRNATY presentation available. Refer to Table 3 for the age-appropriate primary series dosing.

Individuals 12 years of age and older who have partially completed the primary series should receive a single dose of the most current COMIRNATY presentation available.

Individuals who have previously completed a primary series with a COVID-19 vaccine

Individuals 6 months of age and older who have previously completed a primary series should receive a single dose with the most current COMIRNATY presentation at least 3 months after the previous dose.

Individuals may not be protected until 7 days after they have completed their dosing recommendations as noted in Table 3 (see section 5.1).

Additional booster doses in individuals 12 years of age and older

Any subsequent doses of COMIRNATY may be administered at least 3 months after a previous dose of COMIRNATY and in accordance with official recommendations.

Interchangeability with other COVID-19 vaccines

The interchangeability of COMIRNATY with other COVID-19 vaccines has not been established.

Paediatric population

The safety and efficacy of COMIRNATY in paediatric participants aged less than 6 months have not yet been established. Limited data are available.

Elderly population

No dosage adjustment is required in elderly individuals ≥65 years of age. The safety of a booster dose of COMIRNATY in individuals 65 years of age and older is based on safety data in 12 booster dose recipients 65 through 85 years of age in Study 2, 306 booster dose recipients 18 through 55 years of age in Study 2, and 1,175 booster dose recipients 65 years of age and older in Study 4. The effectiveness of a booster dose of COMIRNATY in individuals 65 years of age and older is based on effectiveness data in 306 booster dose recipients 18 through 55 years of age in Study 2, and an efficacy analysis from participants 16 years of age and older in 9,945 participants in Study 4.

Method of administration

Administer COMIRNATY intramuscularly. Do not administer intravascularly, subcutaneously, or intradermally.

- In individuals 6 months to <12 months of age: administer COMIRNATY in the anterolateral aspect of the thigh.
- In individuals 1 year to <5 years of age: administer COMIRNATY in the anterolateral aspect of the thigh or the deltoid muscle.
- In individuals 5 years of age and older: administer COMIRNATY in the deltoid muscle.

For detailed instructions on the handling, dilution, and dose preparation of the vaccine before administration, 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.

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. These cases have primarily occurred within 14 days following vaccination, more often after the second vaccination, and more often, but not exclusively in younger males. There have been reports in females. Based on accumulating data, the reporting rates of myocarditis and pericarditis after primary series in children ages 5 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 and fatal cases have been observed, 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.

Local cases of myocarditis with severe outcomes have been rarely reported with strenuous physical activity following vaccination. Vaccine recipients should be advised to seek medical attention promptly if they develop chest pain, shortness of breath or abnormal heartbeats. Non-specific symptoms of myocarditis and pericarditis also include fatigue, nausea and vomiting, abdominal pain, dizziness or syncope, oedema and cough. Please refer to the national vaccination guidances for local recommendations.

Anxiety-related reactions

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 may be lower in immunosuppressed individuals. Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations.

Duration of protection

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

Limitations of vaccine effectiveness

As with any vaccine, vaccination with COMIRNATY may not protect all vaccine recipients.

4.5 Interaction with other medicinal products and other forms of interaction

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

COMIRNATY 30 micrograms may be administered concomitantly with seasonal influenza vaccine (see section 5.1). Different injectable vaccines should be given at different injection sites.

In individuals 18 years of age and older, COMIRNATY 30 micrograms may be administered concomitantly with a pneumococcal conjugate vaccine (PCV) (see Section 5.1).

In individuals 60 years of age and older, COMIRNATY 30 micrograms may be administered concomitantly with an unadjuvanted recombinant protein respiratory syncytial virus (RSV) vaccine (see Section 5.1).

In individuals 65 years of age and older, COMIRNATY 30 micrograms may be administered concomitantly with an unadjuvanted recombinant protein RSV vaccine and a high dose influenza vaccine (see Section 5.1).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited amount of clinical study data from the use of COMIRNATY (Original) 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 clinical study data are available regarding the use of variant-adapted COMIRNATY during pregnancy.

Breast-feeding

It is unknown whether COMIRNATY is excreted in human milk.

No clinical study data are available regarding the use of variant-adapted COMIRNATY during breast-feeding.

Fertility

It is unknown whether COMIRNATY has an impact on fertility. Animal studies conducted with COMIRNATY (Original) do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of safety profile

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 4,600 participants 5 through <12 years of age. Study 3 also enrolled approximately 3,600 participants 2 through 4 years of age and 2,200 participants 6 months through 23 months of age.

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), 2,408 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.

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.

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

The safety profile in 545 participants 16 years of age and older receiving COMIRNATY (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, 2,260 adolescents [1,131 COMIRNATY (Original); 1,129 placebo] were 12 through 15 years of age. Of these, 1,559 adolescents [786 COMIRNATY (Original) and 773 placebo] were followed for ≥4 months after the second dose.

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; 725 placebo] participants have been followed for ≥4 months after the second dose in the placebo-controlled blinded follow-up period. The safety evaluation in Study 3 is ongoing.

The 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 (≥20%), myalgia, chills and diarrhoea (>10%).

Children 2 through 4 years of age – after 3 doses
In an analysis of Study 3 (Phase 2/3), 3,541 individuals [2,368 COMIRNATY (Original) 3 micrograms and 1,173 placebo] were 2 through 4 years age. Based on data in the blinded placebo-controlled follow-up period up to the cut-off date of 28 February 2023, 1,268 individuals 2 through 4 years of age who received a 3-dose primary course [863 COMIRNATY (Original) 3 micrograms; 405 placebo] have been followed a median of 2.2 months after the third dose.

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

Children 6 through 23 months of age – after 3 doses
In an analysis of Study 3 (Phase 2/3), 2,176 individuals [1,458 COMIRNATY (Original) 3 micrograms and 718 placebo] were 6 through 23 months of age. Based on data in the blinded placebo-controlled follow-up period up to the cut-off date of 28 February 2023, 720 individuals 6 through 23 months of age who received a 3-dose primary course [483 COMIRNATY (Original) 3 micrograms; 237 placebo] have been followed for a median of 1.7 months after the third dose.

The most frequent adverse reactions in children 6 through 23 months of age that received any primary series dose included irritability (>60%), decrease appetite (>30%), tenderness at the injection site (>20%), injection site redness and fever (>10%).

Participants 12 years of age and older – after booster dose
A subset from Study 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 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 (08 February 2022). Of these, 1,281 participants [895 COMIRNATY (Original); 386 placebo] were followed for ≥4 months after the booster dose of COMIRNATY (Original). The overall safety profile for the booster dose was similar to that seen after 2 doses.

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

Children 5 through <12 years of age – after booster dose
In a subset from Study 3, a total of 2,408 children 5 through <12 years of age received a booster dose of COMIRNATY (Original) 10 micrograms at least 5 months (range 5.3 to 19.4 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 28 February 2023 (median follow-up time of 6.4 months).

The most frequent adverse reactions in participants 5 through <12 years of age were injection site pain (>60%), fatigue (>30%), headache (>20%), myalgia, chills, injection site redness, and swelling (>10%).

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

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

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

Table 4: Adverse Reactions from COMIRNATY Clinical Trials and Post-authorisation Experience In Individuals 12 Years of Age and Older*

System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	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]; Cerebral venous thrombosis[d]
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			
Reproductive system and breast disorders						Heavy menstrual bleeding[d]
Infections and infestations				Appendicitis[d]		

* 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 16 years of age and older 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.

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)

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 5: Adverse Reactions from COMIRNATY Clinical Trials and Post-authorisation Experience In Individuals 5 Years Through <12 Years of Age (20 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.

Note: 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.

a. These adverse reactions were identified in the post-authorisation period.
b. The following events are categorised as hypersensitivity reactions: urticaria, pruritus, rash, and angioedema.
c. A higher frequency of lymphadenopathy was observed in participants 5 through <12 years of age in Study 3 (1.9% vs. 0.7%) receiving a booster dose compared to participants receiving 2 doses.

Table 6: Adverse Reactions from COMIRNATY Clinical Trials and Post-authorisation Experience In Individuals 2 Years to <5 Years of Age (28 February 2023 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	
Immune system disorders			Rash[a,b]; Urticaria[a,b]		Anaphylaxis[a]
Metabolism and nutrition disorders				Decreased appetite	
Nervous system disorders		Headache			
Gastrointestinal disorders	Diarrhoea[a]	Vomiting[a]	Nausea		
Musculoskeletal and connective tissue disorders		Arthralgia; Myalgia	Pain in extremity (arm)[a]		
General disorders and administration site conditions	Pyrexia; Injection site pain; Fatigue; Injection site redness	Chills; Injection site swelling		Asthenia	

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

Note: At the time of the data cut-off date, the following reactions were not reported in participants 2 to <5 years of age in Study C4591007: pruritus, angioedema, dizziness, lethargy, myocarditis, pericarditis, hyperhidrosis, night sweats, and malaise but are still considered adverse reactions for this age group.

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

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

Table 7: Adverse Reactions from COMIRNATY Clinical Trials and Post-authorisation Experience In Individuals 6 Months to <2 Years of Age (28 February 2023 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		
Immune system disorders		Rash[a,b]	Urticaria[a,b]		Anaphylaxis[a]
Metabolism and nutrition disorders	Decreased appetite				
Psychiatric disorders	Irritability				
Nervous system disorders			Headache; Lethargy		
Gastrointestinal disorders		Diarrhoea[a]; Vomiting[a]			

System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Not known (cannot be estimated from the available data)
General disorders and administration site conditions	Pyrexia; Injection site tenderness; Injection site redness	Injection site swelling	Fatigue; Chills		

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

Note: At the time of the data cut-off, the following reactions were not reported in participants 6 months to <2 years of age in Study C4591007: pruritus, angioedema, dizziness, myocarditis, pericarditis, nausea, hyperhidrosis, night sweats, myalgia, arthralgia, pain in extremity (arm), malaise, and asthenia but are still considered adverse reactions for this age group.

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

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

Safety with concomitant vaccine administration – COMIRNATY 30 micrograms

Concomitant administration with seasonal influenza vaccine

In Study 8 (C4591030), a Phase 3 study, participants 18 through 64 years of age who received COMIRNATY (Original) co-administered with seasonal inactivated influenza vaccine (SIIV), quadrivalent followed 1 month later by placebo (n=564), were compared to participants who received an inactivated influenza vaccine with placebo followed 1 month later by COMIRNATY (Original) alone (n=564). Reactogenicity events were reported more frequently by participants who received COMIRNATY (Original) co-administered with SIIV, quadrivalent, compared to participants who received COMIRNATY (Original) alone, but overall the reactogenicity events were mostly mild to moderate in severity. The most common adverse reactions reported in the co-administration group versus COMIRNATY (Original) alone were injection site pain (86.2% versus 84.4%, respectively), fatigue (64.0% versus 50.8%, respectively) and headache (47.2% versus 37.8%, respectively).

Concomitant administration with pneumococcal conjugate vaccine

In Study 11 (B7471026), a Phase 3 study, participants 65 years of age and older who received a booster dose of COMIRNATY (Original) co-administered with 20-valent pneumococcal conjugate vaccine (20vPnC [Prevenar® 20]) (n=187), the overall safety profile was similar with COMIRNATY (Original) given alone (n=185). Overall, reactogenicity events were mostly mild to moderate in severity. The most common adverse reactions reported in the co-administration group versus COMIRNATY (Original) alone were injection site pain (72.4% versus 67.6%, respectively), fatigue (54.1% versus 54.6%, respectively), and myalgia (32.4% versus 31.9%, respectively).

Concomitant administration with an RSV vaccine or with an RSV vaccine and a high dose influenza vaccine

In Study 12 (C5481001), a Phase 1/2 study, participants 65 years of age and older who received COMIRNATY (Bivalent BA.4/BA.5) and RSV (bivalent, recombinant [ABRYSVO®]) vaccine co-administered in one arm plus high dose quadrivalent influenza vaccine (QIV [Fluzone® HD]) (n=158) or placebo (n=157) in the opposite arm were compared to participants who received the individual vaccines given with placebo. The overall safety profile was similar with COMIRNATY (Bivalent BA.4/BA.5) given alone (n=150).

Overall, reactogenicity events reported for the concomitantly administered vaccines were mostly mild to moderate in severity. The most common reported adverse reactions in the COMIRNATY (Bivalent

BA.4/BA.5) administered concomitantly with RSV vaccine group, COMIRNATY (Bivalent BA.4/BA.5) administered concomitantly with both RSV vaccine and high dose quadrivalent influenza vaccine group, and COMIRNATY (Bivalent BA.4/BA.5) alone were injection site pain (56.7%, 53.8%, and 62.7%, respectively) and fatigue (38.9%, 46.8%, and 35.3%, respectively).

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

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

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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

Efficacy and immunogenicity

Immunogenicity data supporting the use of a single dose of COMIRNATY in seropositive, vaccine-naïve individuals

In a subset of Study 7 (Study BNT162-17) in participants 18 through 85 years of age, immunogenicity of a single 30 micrograms dose of a Pfizer-BioNTech bivalent COVID-19 vaccine containing equal quantities of modRNA encoding the viral spike (S) glycoprotein for the Alpha and Delta SARS-CoV-2 variants (hereafter referred to as the bivalent Alpha and Delta vaccine which is not authorised or approved) was assessed in COVID-19 vaccine-naïve participants with prior SARS-CoV-2 infection (n=262) compared to participants without prior SARS-CoV-2 infection who received 2 doses of COMIRNATY (Original) in Study 2 (n=275). The immunogenicity of the bivalent Alpha and Delta vaccine is relevant to COMIRNATY (2023-2024 formula) because these vaccines are manufactured using the same process with differences only in the encoded spike proteins.

A primary immunogenicity objective of the study was to assess non-inferiority with respect to level of 50% neutralising titre (NT50) and to the seroresponse rate to the reference strain immune response induced by a single dose of the bivalent Alpha and Delta vaccine in COVID-19 vaccine-naïve participants with evidence of prior infection relative to the response in participants without evidence of SARS-CoV-2 infection who received 2 doses of COMIRNATY (Original).

Non-inferiority of the reference strain immune response with respect to level of NT50 was met, as the lower bound of the 2-sided 95% CI for GMR was >0.67. The GMT was higher after a single dose of bivalent Alpha and Delta vaccine in COVID-19 vaccine-naïve participants with evidence of prior SARS-CoV-2 infection (Table 8).

Non-inferiority of the seroresponse rate to the reference strain was not met, as the lower bound of the 2-sided 95% CIs for the difference in seroresponse rate of reference strain was -10.04%, below the non-inferiority margin of -10% (Table 9).

The immune responses to the Alpha, Delta and Omicron BA.5 variants in vaccine-naïve participants with evidence of prior SARS-CoV-2 infection after 1 dose of the bivalent Alpha and Delta vaccine, in vaccine-naïve participants without evidence of SARS-CoV-2 infection after 2 doses of the bivalent Alpha and Delta vaccine, and in participants who had previously received 2 doses of COMIRNATY (Original) without evidence of SARS-CoV-2 infection and received 1 dose of the bivalent Alpha and Delta vaccine are provided in Table 10.

Table 8: Geometric Mean Ratios – Single Dose of Bivalent Alpha and Delta Vaccine in Vaccine-Naïve Participants With Evidence of Prior SARS-Cov-2 Infection from Study 7 and 2 Doses of COMIRNATY (Original) in Vaccine-Naïve Participants Without Evidence of SARS-Cov-2 Infection from Subset of Study 2 – Reference Strain Neutralisation – Immunogenicity Analysis Set

	Study 7 Single Dose of Bivalent Alpha and Delta Vaccine With Evidence of Prior Infection[a] 3 Weeks After Dose 1[b]		**Study 2 Two Doses of COMIRNATY (Original) Without Evidence of Infection[c] 1 Month After Dose 2[b]**		**Bivalent Alpha and Delta Vaccine With Evidence of Prior Infection[b] / COMIRNATY (Original) Without Evidence of Infection[c]**
SARS-CoV-2 Neutralisation Assay	**n[d]**	**GMT[e] (95% CI[e])**	**n[d]**	**GMT[e] (95% CI[e])**	**GMR[f] (95% CI[f])**
Reference strain - NT50 (titre)[g]	262	17404.2 (15485.1, 19561.1)	275	1328.1 (1183.1, 1491.0)	13.12 (11.14, 15.45)[h]

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

a. Positive N-binding antibody result at baseline, positive NAAT result prior to vaccination, or medical history or adverse event of COVID-19 prior to vaccination.
b. Protocol-specified timing for blood sample collection.
c. Participants who had no serological or virological evidence (up to the 1-month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (i.e., negative N-binding antibody [serum] result at the Dose 1 and 1-month post-Dose 2 visits, negative NAAT [nasal swab] at the Dose 1 and Dose 2 visits, and any unscheduled visit [up to the 1-month post-Dose 2 blood sample collection]) and had no medical history of COVID-19 were included in the analysis.
d. n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.
e. 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.
f. GMRs and 2-sided 95% CIs were calculated by exponentiating the difference of LS means and corresponding CIs based on the analysis of logarithmically transformed neutralising titres using a linear regression model with terms of age, sex, and group. Assay results below the LLOQ were set to 0.5 × LLOQ.
g. SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020]).
h. Non-inferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67.

Table 9: Difference in Percentages of Participants with Seroresponse – Bivalent Alpha and Delta Vaccine in Vaccine-Naïve With Evidence of Prior SARS-CoV-2 Infection from Study 7 and 2 Doses of COMIRNATY (Original Vaccine) Without Evidence of Prior SARS-CoV-2 Infection from Subset of Study 2 – Reference Strain Neutralisation – Immunogenicity Analysis Set

	Study 7 Bivalent Alpha and Delta Vaccine With Evidence of Prior Infection[a] 3 Weeks After Dose 1[b]		Study 2 COMIRNATY (Original) Without Evidence of Prior Infection[c] 1 Month After Dose 2[b]		Bivalent Alpha and Delta Vaccine With Evidence of Prior Infection[a] Minus COMIRNATY (Original) Without Evidence of Prior Infection[c]	
SARS-CoV-2 Neutralisation Assay	**N[d]**	**n[e] (%) (95% CI[f])**	**N[d]**	**n[e] (%) (95% CI[f])**	**Difference %[g]**	**95% CI[h]**
Reference strain - NT50 (titre)[i]	260	223 (85.8) (80.9, 89.8)	275	249 (90.5) (86.5, 93.7)	-4.55	(-10.04, 0.83)[j]

Abbreviations: CI = confidence interval; N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralising titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

a. Positive N-binding antibody result at baseline, positive NAAT result prior to vaccination, or medical history or adverse event of COVID-19 prior to vaccination.
b. Protocol-specified timing for blood sample collection.
c. Participants who had no serological or virological evidence (up to the 1-month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (i.e., negative N-binding antibody [serum] result at the Dose 1 and 1-month post-Dose 2 visits, negative NAAT [nasal swab] at the Dose 1 and Dose 2 visits, and any unscheduled visit [up to the 1-month post-Dose 2 blood sample collection]) and had no medical history of COVID-19 were included in the analysis.
d. 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.
e. n = Number of participants with seroresponse for the given assay at the given sampling time point.
f. Exact 2-sided CI, based on the Clopper and Pearson method.

g. Adjusted difference in proportions estimated using minimum risk weights and stratified by sex and age group (18 to 55 years, 56 to 85 years), expressed as a percentage.
h. 2-sided CI based on the Newcombe method stratified by sex and age group (18 to 55 years, 56 to 85 years) with minimum risk weights for the difference in proportions.
i. SARS-CoV-2 NT50 were determined using a validated 384-well assay platform (original strain [USA-WA1/2020, isolated in January 2020]).
j. Non-inferiority is declared if the lower bound of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is >-10%.

Table 10: Geometric Mean Titres – Bivalent Alpha and Delta Vaccine in Vaccine-Naïve and Vaccine-Experienced Participants from Study 7 – Variant Neutralisation – Immunogenicity Analysis Set

		Bivalent Alpha and Delta Vaccine					
		Single Dose in Vaccine-Naïve With Evidence of Prior Infection[a]		Two Doses in Vaccine-Naïve Without Evidence of Infection[b]		One Dose in Participants Who Previously Received 2 Doses of COMIRNATY (Original) Without Evidence of Infection[b]	
SARS-CoV-2 Neutralisation Assay	Sampling Time Point[c]	n[d]	GMT[e] (95% CI[e])	n[d]	GMT[e] (95% CI[e])	n[d]	GMT[e] (95% CI[e])
Alpha – NT50 (titre)[f]	Pre-vaccination	142	55.7 (41.2, 75.4)	17	8.5 (4.1, 17.4)	136	9.3 (7.8, 11.2)
	Post-vaccination	142	1045.3 (853.1, 1280.8)	17	180.8 (91.8, 356.3)	136	749.5 (621.1, 904.6)
Delta – NT50 (titre)[f]	Pre-vaccination	142	45.1 (33.7, 60.3)	17	6.9 (4.2, 11.3)	136	8.1 (6.9, 9.5)
	Post-vaccination	142	859.9 (693.4, 1066.4)	17	62.6 (30.9, 127.0)	136	466.6 (401.8, 541.9)
Omicron BA.5 – NT50 (titre)[f]	Pre-vaccination	142	16.0 (12.7, 20.2)	17	5.4 (4.6, 6.4)	136	5.6 (5.2, 6.1)
	Post-vaccination	142	229.3 (191.7, 274.4)	17	10.2 (5.7, 18.3)	136	80.8 (66.9, 97.6)

Abbreviations: CI = confidence interval; CPE = cytopathic effect; 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; ULOQ = upper limit of quantitation.

a. Positive N-binding antibody result at baseline, positive NAAT result prior to vaccination, or medical history or adverse event of COVID-19 prior to vaccination.
b. Participants who had no serological or virological evidence (up to the 1-month post-Dose 2 blood sample collection for vaccine-naïve and up to the 1-month post-study vaccination blood sample collection for vaccine-experienced) of past SARS-CoV-2 infection (i.e., negative N-binding antibody [serum] result and negative NAAT [oral swab] at all planned visits and any unscheduled visit [up to the 1-month post-Dose 2 blood sample collection for vaccine-naïve and 1-month post-study vaccination blood sample collection for vaccine-experienced]) and had no medical history or adverse event of COVID-19 (up to the 1-month post-Dose 2 blood sample collection for vaccine-naïve and 1-month post-study vaccination blood sample collection for vaccine-experienced) were included in the analysis.
c. Protocol-specified timing for blood sample collection: 3 weeks after a single dose in vaccine-naïve with evidence of prior SARS-CoV-2 infection, one month after 2 doses in vaccine-naïve without evidence of SARS-CoV-2 infection, one month after a single dose in participants who previously received 2 doses of COMIRNATY (original vaccine) without evidence of SARS-CoV-2 infection.
d. n = Number of participants with valid and determinate assay results for the specified assay at the given sampling time point.

e. 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; assay results above the ULOQ were set to ULOQ.
f. SARS-CoV-2 NT50 were determined using validated assays for 50% SARS-CoV-2 neutralising titres against Alpha (B.1.1.7), Delta (B1.617.2), and Omicron BA.5 (B.1.1.529.5) using clinical SARS-CoV-2 isolates in a CPE-based microneutralisation assay.

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

Table 11: Demographics (Population for the Primary Efficacy Endpoint)[a]

	COMIRNATY (Original) (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/m^2)
   - 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 (Original) 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/m^2, chronic pulmonary disease, diabetes mellitus, hypertension].

The vaccine efficacy information is presented in Table 12.

Table 12: 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

First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection*			
Subgroup	**COMIRNATY (Original) 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)
First COVID-19 occurrence from 7 days after Dose 2 in participants with or without* evidence of prior SARS-CoV-2 infection			
Subgroup	**COMIRNATY (Original) N[a]=19,965 Cases n1[b] Surveillance Time[c] (n2[d])**	**Placebo N[a]=20,172 Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI[e])**
All participants	9 2.332 (18,559)	169 2.345 (18,708)	94.6 (89.9, 97.3)
16 through 64 years	8 1.802 (14,501)	150 1.814 (14,627)	94.6 (89.1, 97.7)
65 years and older	1 0.530 (4044)	19 0.532 (4067)	94.7 (66.8, 99.9)
65 through 74 years	1 0.424 (3239)	14 0.423 (3255)	92.9 (53.2, 99.8)
75 years and older	0 0.106 (805)	5 0.109 (812)	100.0 (-12.1, 100.0)

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

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

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

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

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

d. n2 = Number of participants at risk for the endpoint.
e. 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 13 March 2021, representing up to 6 months of follow-up after Dose 2 for participants in the efficacy population.

The updated vaccine efficacy information is presented in Table 13.

Table 13: 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 (Original) N[a]=20,998 Cases n1[b] Surveillance Time[c] (n2[d])**	**Placebo N[a]=21,096 Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI[e])**
All participants[f]	77 6.247 (20,712)	850 6.003 (20,713)	91.3 (89.0, 93.2)
16 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 (Original) 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])**
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 (Original) 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 14 and Table 15.

Table 14: 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 (Original) 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)

Subgroup	COMIRNATY (Original) N[a]=20,998 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=21,096 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI[e])
All 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)
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 (Original) 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.

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. All others = American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported race categories.

Table 15: 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 (Original) 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])
Sex			
Male	44	411	89.9

	3.376 (11,103)	3.181 (10,920)	(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)
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 (Original) 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.

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. 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 16 and Table 17.

Table 16: 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 (Original) 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])
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 (Original) 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])

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/m^2 or BMI ≥95th percentile [12 through 15 Years of age]).
h. Obese is defined as BMI ≥30 kg/m^2. 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 17: 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 (Original) 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])
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)

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.

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 for surveillance time.
f. Included confirmed cases in participants 12 through 15 years of age: 0 in the COMIRNATY (Original) group; 18 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/m^2 or BMI ≥95th percentile [12 through 15 years of age]).
h. Obese is defined as BMI ≥30 kg/m^2. 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 18) 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 (Original) and placebo groups.

Table 18: Vaccine Efficacy – First Severe COVID-19 Occurrence in Participants With or Without* Prior SARS-CoV-2 Infection Based on FDA† or Centres 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 (Original) Cases n1[a] Surveillance Time (n2[b])	**Placebo Cases n1[a] Surveillance Time (n2[b])**	**Vaccine Efficacy % (95% CI[c])**
After Dose 1[d]	1 8.439[e] (22,505)	30 8.288[e] (22,435)	96.7 (80.3, 99.9)
7 days after Dose 2[f]	1 6.522[g] (21,649)	21 6.404[g] (21,730)	95.3 (70.9, 99.9)

Vaccine Efficacy – First Severe COVID-19 Occurrence Based on CDC Definition			
	COMIRNATY (Original) 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[e] (22,473)	45 8.269[e] (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 ≤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, non-invasive 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 1005 participants who received the vaccine and 16 cases out of 978 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 75.3, 100.0). In participants with or without evidence of prior infection there were 0 cases in the 1119 who received

vaccine and 18 cases in 1110 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 78.1, 100.0).

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 19.

Table 19: Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2: Without Evidence of Infection and With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-up Period, Adolescents 12 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 (Original) N[a]=1057 Cases n1[b] Surveillance Time[c] (n2[d])	**Placebo N[a]=1030 Cases n1[b] Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI[e])**
Adolescents 12 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 (Original) 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.

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 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 8 October 2021.

Table 20 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 20: 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 (Original) 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%
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)

a. 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.
b. n = Number of participants with the specified characteristic.
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: defined as participants who had at least 1 of the prespecified comorbidities based on MMWR 69(32);1081-1088 and/or obesity (BMI ≥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 21. None of the cases accrued met criteria for severe COVID-19 or multisystem inflammatory syndrome in children (MIS-C). No cases of COVID-19 were observed in either the vaccine group or the placebo group in participants with evidence of prior SARS-CoV-2 infection.

Table 21: Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2: Without Evidence of Infection Prior to 7 Days After Dose 2 – Phase 2/3 – Children 5 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 (Original) 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.

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.

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 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 22.

Table 22: 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 (Original)			
		10 micrograms /Dose 5 Through <12 Years n[a]=264	30 micrograms /Dose 16 Through 25 Years n[a]=253	5 Through <12 Years/ 16 Through 25 Years	
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; Y/N = yes/no.

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

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

Among participants without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, 99.2% of children 5 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 23.

Table 23: Difference in Percentages of Participants With Seroresponse – Participants Without* Evidence of Infection up to 1 Month After Dose 2 – Immunobridging Subset – Phase 2/3 – Comparison of 5 Through <12 Years of Age to Study 2 Phase 2/3 16 Through 25 Years of Age – Evaluable Immunogenicity Population

		COMIRNATY (Original)			
		Study 3 10 micrograms /Dose 5 Through <12 Years N[a]=264	Study 2 30 micrograms /Dose 16 Through 25 Years N[a]=253	5 Through <12 Years/ 16 Through 25 Years	
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; Y/N = yes/no.

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

a. N = Number of participants with valid and determinate assay results both before vaccination and at 1 month after Dose 2. These values are the denominators for the percentage calculations.
b. Protocol-specified timing for blood sample collection.
c. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.
d. Exact 2-sided CI based on the Clopper and Pearson method.
e. Difference in proportions, expressed as a percentage (Group 1 [5 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.

Efficacy and immunogenicity in individuals 6 months through <5 years of age – 3-dose primary course

Effectiveness in individuals 6 months through 4 years of age is based on a comparison of efficacy against symptomatic COVID-19 comparing to placebo and immune responses in this age group to individuals 16 through 25 years of age.

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

The efficacy analysis of Study 3 was performed across the combined population of participants 6 months through 4 years of age based on cases confirmed among 873 participants in the

COMIRNATY (Original) group and 381 participants in the placebo group (2:1 randomisation ratio) who received all 3 doses of study intervention during the blinded follow-up period when the Omicron variant of SARS-CoV-2 (BA.2) was the predominant variant in circulation (data cut-off date of 17 June 2022).

Table 24 presents the specific demographic characteristics in participants 6 months through 4 years of age who received 3 doses of COMIRNATY (Original) (3 micrograms modRNA) or placebo.

Table 24: Demographics Characteristics – Participants Without Evidence of Infection Prior to 7 Days After Dose 3 – Blinded Follow-Up Period – Phase 2/3 – 6 Months through 4 Years of Age – Evaluable Efficacy (3-Dose) Population

	COMIRNATY (Original) 3 micrograms/Dose (N[a]=873) n[b] (%)	**Placebo (N[a]=381) n[b] (%)**
Sex		
Male	427 (48.9)	173 (45.4)
Female	446 (51.1)	208 (54.6)
Race		
White	666 (76.3)	296 (77.7)
Black or African American	30 (3.4)	12 (3.1)
American Indian or Alaska Native	2 (0.2)	0
Asian	87 (10.0)	38 (10.0)
Native Hawaiian or other Pacific Islander	0	1 (0.3)
Other[c]	88 (10.1)	34 (8.9)
Ethnicity		
Hispanic or Latino	98 (11.2)	27 (7.1)
Not Hispanic or Latino	774 (88.7)	354 (92.9)
Not reported	1 (0.1)	0
Comorbidities[d]		
Yes	76 (8.7)	37 (9.7)
No	797 (91.3)	344 (90.3)

Abbreviations: BMI = body mass index; MMWR = Morbidity and Mortality Weekly Report; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein-binding; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

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

a. N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
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: defined as participants who had at least one of the prespecified comorbidities based on MMWR 69(32);1081-8 and/or obesity (BMI ≥95th percentile) for 2 to <5 years.

The vaccine efficacy results after Dose 3 in participants 6 months through 4 years of age are presented in Table 25.

Table 25: Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 3 – Blinded Follow-Up Period – Participants Without Evidence of Infection and Participants With or Without Evidence of Infection Prior to 7 Days After Dose 3 – Phase 2/3 – 6 Months Through 4 Years of Age – Evaluable Efficacy (3-Dose) Population

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

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

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

a. N = number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1,000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 3 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Two-sided 95% confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.

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

Among participants 2 through 4 years of age, severe COVID-19 criteria (as described in the protocol, based on FDA definition and modified for children) were fulfilled for 9 cases [6 COMIRNATY (Original) and 3 placebo] of which 5 of the 6 cases in the COMIRNATY (Original) group fulfilled a

single criterion of increased heart rate or respiratory rate and all 3 cases in the placebo group fulfilled a single criterion of increased heart rate or decreased peripheral oxygen saturation. None of the cases accrued met criteria for multisystem inflammatory syndrome in children (MIS-C).

Among participants 6 months through 23 months of age, severe COVID-19 criteria were fulfilled for 3 cases [2 COMIRNATY (Original) and 1 placebo] of which 1 of the 2 cases in the COMIRNATY (Original) group fulfilled a single criterion of increased heart rate (152 bpm) and 1 case in the placebo group fulfilled a single criterion of increased heart rate (172 bpm). None of the cases accrued met criteria for MIS-C.

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

Table 26 presents the specific demographic characteristics in the studied evaluable immunogenicity population.

Table 26: Demographics Characteristics – Immunobridging Subset – Participants 2 Through 4 Years of Age (Study 3) and Participants 16 Through 25 Years of Age (Study 2) – Without Evidence of Infection -Evaluable Immunogenicity Population

	COMIRNATY (Original) 3 micrograms/Dose 2 Through 4 Years of Age (N[a]=143) n[b] (%)	**COMIRNATY (Original) 30 micrograms/Dose 16 Through 25 Years of Age (N[a]=170) n[b] (%)**
Sex		
Male	63 (44.1)	79 (46.5)
Female	80 (55.9)	91 (53.5)
Age at Vaccination (years)		
Mean (SD)	2.7 (0.76)	21.2 (2.95)
Median	3.0	2.0
Min, max	(2, 4)	(16, 25)
Race		
White	99 (69.2)	130 (76.5)
Black or African American	8 (5.6)	15 (8.8)
American Indian or Alaska Native	0	3 (1.8)
Asian	16 (11.2)	13 (7.6)
Native Hawaiian or other Pacific Islander	0	1 (0.6)
Other[c]	20 (14.0)	8 (4.7)
Ethnicity		
Hispanic or Latino	16 (11.2)	51 (30.0)
Not Hispanic or Latino	126 (88.1)	119 (70.0)
Not reported	1 (0.7)	0

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

a. N = Number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.

c. Includes multiracial and not reported.

SARS-CoV-2 NT50 were compared between an immunogenicity subset of Phase 2/3 participants 2 through 4 years of age from Study 3 at 1 month after the 3-dose primary course and a randomly selected subset from Study 2 (Phase 2/3) participants 16 through 25 years of age at 1 month after the 2-dose primary course, using a microneutralisation assay against the reference strain (USA_WA1/2020). The primary immunobridging analyses compared the geometric mean titres (using a GMR) and the seroresponse (defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from before Dose 1) rates in the evaluable immunogenicity population of participants without evidence of prior SARS-CoV-2 infection up to 1 month after Dose 3 in participants 2 through 4 years of age and up to 1 month after Dose 2 in participants 16 through 25 years of age. The prespecified immunobridging criteria were met for both the GMR and the seroresponse difference (Table 27 and Table 28, respectively).

Table 27: SARS-CoV-2 GMTs (NT50) at 1 Month After Vaccination Course – Immunobridging Subset - Participants 2 Through 4 Years of Age (Study 3) 1 Month After Dose 3 and Participants 16 Through 25 Years of Age (Study 2) 1 Month After Dose 2 – Without Evidence of SARS-CoV-2 Infection – Evaluable Immunogenicity Population

	COMIRNATY (Original)		
	3 micrograms/Dose 2 Through 4 Years of Age (1 month After Dose 3) n[a]=143	30 micrograms/Dose 16 Through 25 Years of Age (1 Month After Dose 2) n[a]=170	GMR (95%CI) (2 Through 4 Years of Age/16 Through 25 Years of Age)[c,d]
Assay	GMT[b] (95% CI[b])	GMT[b] (95% CI[b])	
SARS-CoV-2 neutralisation assay - NT50 (titre)[e]	1535.2 (1388.2, 1697.8)	1180.0 (1066.6, 1305.4)	1.30 (1.13, 1.50)

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

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

a. n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
b. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
c. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (2 to 4 years of age minus 16 to 25 years of age) and the corresponding CI (based on the Student t distribution).
d. Immunobridging is declared if the lower bound of the 2-sided 95% CI for the GMR ratio is greater than 0.67 and the point estimate of the GMR is ≥0.8.
e. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralisation Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralisation is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralised.

Table 28: Difference in Percentages of Participants With Seroresponse at 1 Month After Vaccination Course – Immunobridging Subset – Participants 2 Through 4 Years of Age (Study 3) 1 Month After Dose 3 and Participants 16 Through 25 Years of Age (Study 2) 1 Month After Dose 2 Without Evidence of Infection – Evaluable Immunogenicity Population

	COMIRNATY (Original)		Difference in Seroresponse Rates %[d] (95% CI[e]) (2 Through 4 Years of age Minus 16 Through 25 Years of Age)[f]
	3 micrograms/Dose 2 Through 4 Years of Age (1 Month After Dose 3) N[a]=141	30 micrograms/Dose 16 Through 25 Years of Age (1 Month After Dose 2) N[a]=170	
Assay	n[b] (%) (95% CI[c])	n[b] (%) (95% CI[c])	
SARS-CoV-2 neutralisation assay - NT50 (titre)[g]	141 (100.0) (97.4, 100.0)	168 (98.8) (95.8, 99.9)	1.2 (-1.5, 4.2)

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

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

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

a. N = Number of participants with valid and determinate assay results both before vaccination and at 1 month after Dose 2. These values are the denominators for the percentage calculations.
b. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.
c. Exact 2-sided CI based on the Clopper and Pearson method.
d. Difference in proportions, expressed as a percentage (2 through 4 years of age minus 16 through 25 years of age).
e. 2-sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
f. Immunobridging is declared if the lower bound of the 2-sided 95% CI for the difference in proportions is greater than -10.0% provided that the immunobridging criteria based on GMR were met.
g. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralisation Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralisation is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralised.

Using a non-validated fluorescence focus reduction neutralisation test assay against the Omicron variant of SARS-CoV-2 (BA.1), the NT50 GMT at 1 month after Dose 3 among a subset of 34 study participants without evidence of prior SARS-CoV-2 infection (82.5 [2-sided 95% CI: 55.4, 122.9]) was increased compared to the NT50 GMT before Dose 3 (14.0 [2-sided 95% CI: 10.6, 18.5]).

An additional descriptive immunogenicity analysis was performed for participants 2 through 4 years of age who received a 3-dose course of COMIRNATY (Original) in Study 3 (Phase 2/3), compared with a subset of participants 18 through 50 years of age in Study C4591017 (Phase 3) who had received a 2-dose primary course followed by a booster dose of COMIRNATY (Original) 30 micrograms. The comparator group (participants 18 through 50 years of age) in this analysis had a similar interval between COMIRNATY (Original) Dose 2 and Dose 3 (median 13.0 weeks) as the participants 2 to 4 years of age (median 10.6 weeks). Among 34 participants 2 through 4 years of age without evidence of prior SARS-CoV-2 infection who received 3 doses of COMIRNATY (Original)

3 micrograms, neutralising GMTs were 114.3 at 1-month post-Dose 3. Among 27 participants 18 through 50 years of age without evidence of prior SARS-CoV-2 infection who received 3 doses of COMIRNATY (Original) 30 micrograms, Omicron neutralising GMTs were 164.2 at 1-month post Dose 3.

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

Table 29 presents the specific demographic characteristics in the studied evaluable immunogenicity population.

Table 29: Demographics Characteristics – Immunobridging Subset – Participants 6 Through 23 Months of Age (Study 3) and Participants 16 Through 25 Years of Age (Study 2) – Without Evidence of Infection -Evaluable Immunogenicity Population

	COMIRNATY (Original) 3 micrograms/Dose 6 Through 23 Months of Age (N[a]=82) n[b] (%)	**COMIRNATY (Original) 30 micrograms/Dose 16 Through 25 Years of Age (N[a]=170) n[b] (%)**
Sex		
Male	51 (62.2)	79 (46.5)
Female	31 (37.8)	91 (53.5)
Age at Vaccination (years)		
Mean (SD)	15.7 (4.84)	21.2 (2.95)
Median	16.0	2.0
Min, max	(6, 23)	(16, 25)
Race		
White	59 (72.0)	130 (76.5)
Black or African American	1 (1.2)	15 (8.8)
American Indian or Alaska Native	1 (1.2)	3 (1.8)
Asian	11 (13.4)	13 (7.6)
Native Hawaiian or other Pacific Islander	0	1 (0.6)
Other[c]	10 (12.2)	8 (4.7)
Ethnicity		
Hispanic or Latino	13 (15.9)	51 (30.0)
Not Hispanic or Latino	69 (84.1)	119 (70.0)

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

a. N = Number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. Includes multiracial and not reported.

SARS-CoV-2 NT50 1 month after the vaccination course were compared between an immunogenicity subset of Phase 2/3 participants 6 through 23 months of age from Study 3 and a randomly selected subset from Study 2 (Phase 2/3) participants 16 through 25 years of age, using a microneutralisation assay against the reference strain (USA_WA1/2020). The primary immunobridging analyses

compared the geometric mean titres (using a GMR) and the seroresponse (defined as achieving at least 4-fold rise in SARS-CoV-2 NT50 from before Dose 1) rates in the evaluable immunogenicity population of participants without evidence of prior SARS-CoV-2 infection up to 1 month after Dose 3 in participants 6 through 23 months of age and up to 1 month after Dose 2 in participants 16 through 25 years of age. The prespecified immunobridging criteria were met for both the GMR and the seroresponse difference (Table 30 and Table 31, respectively).

Table 30: SARS-CoV-2 GMTs (NT50) at 1 Month After Vaccination Course – Immunobridging Subset - Participants 6 Through 23 Months of Age (Study 3) 1 Month After Dose 3 and Participants 16 Through 25 Years of Age (Study 2) 1 Month After Dose 2 – Without Evidence of SARS-CoV-2 – Evaluable Immunogenicity Population

	COMIRNATY (Original)		
	3 micrograms/Dose 6 Through 23 Months of Age (1 Month After Dose 3) n[a]=82	30 micrograms/Dose 16 Through 25 Years of Age (1 Month After Dose 2) n[a]=170	GMR (95%CI) (6 Through 23 Months of Age/16 Through 25 Years of Age)[c,d]
Assay	GMT[b] (95% CI[b])	GMT[b] (95% CI[b])	
SARS-CoV-2 neutralisation assay - NT50 (titre)[e]	1406.5 (1211.3, 1633.1)	1180.0 (1066.6, 1305.4)	1.19 (1.00, 1.42)

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

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

a. n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
b. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titres and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
c. GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titres (6 through 23 months of age minus 16 through 25 years of age) and the corresponding CI (based on the Student t distribution).
d. Immunobridging is declared if the lower bound of the 2-sided 95% CI for the GMR ratio is greater than 0.67 and the point estimate of the GMR is ≥0.8.
e. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralisation Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralisation is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralised.

Table 31: Difference in Percentages of Participants With Seroresponse at 1 Month After Vaccination Course – Immunobridging Subset – Participants 6 Through 23 Months of Age (Study 3) 1 Month After Dose 3 and Participants 16 Through 25 Years of Age (Study 2) to 1 Month After Dose 2 Without Evidence of Infection – Evaluable Immunogenicity Population

	COMIRNATY (Original)		Difference in Seroresponse Rates %[d] (95% CI[e]) (6 Through 23 Months of Age Minus 16 Through 25 Years of Age)[f]
	3 micrograms/Dose 6 Through 23 Months of Age (1 Month After Dose 3) N[a]=80	30 micrograms/Dose 16 Through 25 Years of Age (1 Month After Dose 2) N[a]=170	
Assay	n[b] (%) (95% CI[c])	n[b] (%) (95% CI[c])	
SARS-CoV-2 neutralisation assay - NT50 (titre)[g]	80 (100.0) (95.5, 100.0)	168 (98.8) (95.8, 99.9)	1.2 (-3.4, 4.2,)

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

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

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

a. N = Number of participants with valid and determinate assay results both before vaccination and at 1 month after Dose 2. These values are the denominators for the percentage calculations.
b. n = Number of participants with seroresponse for the given assay at the given dose/sampling time point.
c. Exact 2-sided CI based on the Clopper and Pearson method.
d. Difference in proportions, expressed as a percentage (6 through 23 months of age minus 16 through 25 years of age).
e. 2-sided CI, based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
f. Immunobridging is declared if the lower bound of the 2-sided 95% CI for the difference in proportions is greater than -10.0% provided that the immunobridging criteria based on GMR were met.
g. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralisation Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralisation is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralised.

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

An additional descriptive immunogenicity analysis was performed for participants 6 through 23 months of age who received a 3-dose course of COMIRNATY (Original) in Study 3 (Phase 2/3), compared with a subset of participants 18 through 50 years of age in Phase 3 Study C4591017 who had received a 2-dose primary course followed by a booster dose of COMIRNATY (Original) 30 micrograms. The comparator group (participants 18 through 50 years of age) in this analysis had a similar interval between COMIRNATY (Original) Dose 2 and Dose 3 (median 13.0 weeks) as the participants 6 through 23 months of age (median 12.9 weeks). Among 32 participants 6 through 23 months of age without evidence of prior SARS-CoV-2 infection who received 3 doses of COMIRNATY (Original) 3 micrograms, Omicron neutralising GMTs were 128.8 at 1-month post-

Dose 3. Among 27 participants 18 through 50 years of age without evidence of prior SARS-CoV-2 infection who received 3 doses of COMIRNATY (Original) 30 micrograms, Omicron neutralising GMTs were 164.2 at 1-month post-Dose 3.

Immunogenicity in participants 18 years of age and older – after booster dose
Effectiveness of a booster dose of COMIRNATY (Original) 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 32 and Table 33).

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 32: 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±

		COMIRNATY (Original) Sampling Time Point			
		1 Month After Booster Dose	1 Month After Dose 2	1 Month After Booster Dose - 1 Month After Dose 2	Met Non-inferiority Objective[d] (Y/N)
Assay	n[a]	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)[e]	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 (Original)] 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 (Original) 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 (Original), 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 33: Percentage Difference of Participants Achieving Seroresponse – 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±

		COMIRNATY (Original) 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		
Assay	N[a]	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: Seroresponse is defined as achieving a ≥4-fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a post-vaccination assay result ≥4 × LLOQ is considered a seroresponse.
* 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 (Original) 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 (Original), 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 seroresponse for the given assay at the given dose/sampling time point.
c. Exact 2-sided CI based on the Clopper and Pearson method.
d. Difference in proportions, expressed as a percentage (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 08 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 (Original) 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 34.

Table 34: 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 (Original) 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 (Original) 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 (Original) 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 (Original) 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 35.

Table 35: 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 (Original) 10 micrograms/Dose					
		3-Dose Set		2-Dose Set		Total	
Assay	Dose/ Sampling Time Point[a]	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])
SARS-CoV-2 neutralisation assay - NT50 (titre)	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)

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 15 March 2022. Among those, 30 had blood sample collection at 1-month post-Dose 2. Two-dose immunogenicity set included an extra 67 participants randomly selected from previous Dose-2 evaluable immunogenicity population and without evidence of infection up to 1-month post-Dose 2 subset used for 2-dose immunobridging analysis.

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

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

Immunogenicity in children 5 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 36).

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 36: 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 (Original) 10 micrograms/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.

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

Immunogenicity with concomitant vaccine administration – COMIRNATY 30 micrograms

Concomitant administration with seasonal influenza vaccine

In Study 8 (C4591030), a Phase 3 multicentre, randomised, observer-blind study, 1,134 participants 18 through 64 years of age who had received 3 doses of COMIRNATY (Original) at least 3 months prior were randomised in a 1:1 ratio to receive either COMIRNATY (Original) co-administered with

a seasonal inactivated influenza vaccine (SIIV), quadrivalent (Afluria Quad) followed 1 month later by placebo (Group 1, n=568) or an inactivated influenza vaccine with placebo followed 1 month later with COMIRNATY (Original) (Group 2, n=566).

The immune responses to COMIRNATY (Original) and SIIV were similar after COMIRNATY (Original) administered concomitantly with SIIV compared with those elicited by either vaccine administered alone. The non-inferiority criterion was achieved for both full-length S-binding immunoglobulin G (IgG) and all 4 influenza strain-specific haemagglutination inhibition (HAI) titres.

The immunogenicity results are presented in Table 37 and Table 38.

Table 37: Geometric Mean Ratio for Full-Length S-Binding IgG Levels (U/mL) at 1 Month After BNT162b2 Vaccination – Evaluable BNT162b2 Immunogenicity Population

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

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

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

Table 38: Geometric Mean Ratio for Strain-Specific HAI Titres at 1 Month After SIIV Vaccination – Evaluable SIIV Immunogenicity Population

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

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

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

Concomitant administration with pneumococcal conjugate vaccine

In Study 11 (B7471026), a double-blind, randomised descriptive study, participants 65 years of age and older who had received 2 doses of COMIRNATY (Original) at least 6 months earlier, were randomised in a 1:1:1 ratio to receive either 20vPnC concomitantly administered with a booster dose of COMIRNATY (Original) (n=190), or 20vPnC vaccine administered alone (n=191), or a booster dose of COMIRNATY (Original) administered alone (n=189).

Immune responses to both vaccines were observed after concomitant administration of 20vPnC vaccine and COMIRNATY (Original). Opsonophagocytic activity (OPA) GMTs for the 20 pneumococcal serotypes were similar to 20vPnC vaccine administered alone and IgG GMCs for the full-length S−binding protein were similar to COMIRNATY (Original) administered alone. A post-hoc analysis found the immune responses to all 20 serotypes elicited by 20vPnC vaccine when concomitantly administered with COMIRNATY (Original) would have met conventional 2-fold non-inferiority criteria compared to 20vPnC vaccine alone, and the full-length S-binding IgG GMC elicited by COMIRNATY (Original) would have met conventional 1.5-fold non-inferiority criteria compared to COMIRNATY (Original) alone.

Concomitant administration with an RSV vaccine or with an RSV vaccine and a high dose influenza vaccine

In Study 12 (C5481001) a Phase 1/2, randomised, multicentre, parallel group, observer-blinded study 1,083 participants 65 years of age and older who had previously received at least 3 prior doses of an mRNA COVID-19 vaccine, had not previously received any RSV vaccine, or an influenza vaccine in the ≤120 days prior to enrolment, were randomised in 1 of 2 enrolment strata.

The first stratum of approximately 750 participants were randomised 1:1 to evaluate the safety, tolerability, and immunogenicity of admixed COMIRNATY (Bivalent BA.4/BA.5) and RSV (bivalent, recombinant) vaccine concomitantly administered with high dose quadrivalent flu vaccine or placebo in the opposite arm, compared to the individual vaccines.

In the second stratum (total participants n=316) participants were randomised 1:1 to receive COMIRNATY (Bivalent BA.4/BA.5) with concomitantly administered RSV (bivalent, recombinant) vaccine (in one arm) with either placebo or high dose quadrivalent flu vaccine (opposite arm). The study objectives included assessing the impact on the immune response of COMIRNATY (Bivalent BA.4/BA.5) concomitantly administered with RSV (bivalent, recombinant) vaccine, the immune response of concomitant use of RSV (bivalent, recombinant) vaccine, COMIRNATY (Bivalent BA.4/BA.5), and high dose quadrivalent flu vaccine.

When COMIRNATY (Bivalent BA.4/BA.5) was concomitantly administered with RSV (bivalent, recombinant) vaccine immunologic non-inferiority was demonstrated for COMIRNATY (Bivalent

BA.4/BA.5) and RSV (bivalent, recombinant) vaccine compared to individual administration. The lower limit of the 2 sided 97.5% CI for the GMR for RSV A, RSV B, both SARS-CoV-2 Omicron BA.4/BA.5 strain and SARS-COV-2 Wuhan-Hu 1 strain (wildtype) reference strain neutralising titres (NTs) all met the predefined 2-fold non-inferiority criterion.

When COMIRNATY (Bivalent BA.4/BA.5) and RSV (bivalent, recombinant) vaccine were concomitantly administered with high dose quadrivalent flu vaccine, immunologic non-inferiority was demonstrated for COMIRNATY (Bivalent BA.4/BA.5), RSV (bivalent, recombinant) vaccine and high dose quadrivalent flu vaccine group compared to each individual administration. The lower limit of the 2 sided 97.5% CI for the GMR for RSV A, RSV B, both SARS-CoV-2 Omicron BA.4/BA.5 strain and SARS-COV-2 Wuhan-Hu 1 strain (wildtype) reference strain NTs, and each of the 4 strain specific HAI titres all met the predefined 2-fold non-inferiority criterion.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data with COMIRNATY (Original) 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

Vials

Shelf life of frozen vials

COMIRNATY may 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.

If COMIRNATY is received frozen at -90 °C to -60 °C the frozen vials can continue to be stored at -90 °C to -60 °C according to the table below.

COMIRNATY Variant	**Vaccine Presentation(s) Vial Cap and Vial Label Colour**	**Shelf Life of Unopened Frozen Vials When Stored at -90 °C to -60 °C**
COMIRNATY (Omicron JN.1)	Yellow (3 micrograms)	18 months
	Blue[a] (10 micrograms)	18 months
	Grey[a] (30 micrograms)	18 months

a. Refers to either the single dose vial presentation for the light blue and light grey caps or the multidose vial presentation for the dark blue and dark grey caps.

Thawing frozen vials

- Frozen (-90 °C to -60 °C) vials can be thawed at either 2 °C to 8 °C or at temperatures up to 30 °C (see section 6.6 for more detailed thawing instructions).
- **Once thawed, the vaccine should not be re-frozen.**

Shelf life of refrigerated vials

- Frozen vials may be transferred to refrigerated storage (2 °C to 8 °C) upon receipt. Once moved to refrigerated storage, unopened vials may be stored for a single period of up to 10 weeks, not exceeding the original expiry date (EXP).
- Upon moving the product to 2 °C to 8 °C storage, the original expiry date on the outer carton should be crossed out and updated expiry date must be written (10 weeks from the date the vials were removed from frozen storage). The vaccine should be used or discarded by the updated expiry date.
- If the vaccine is received refrigerated (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.

Storage of thawed, opened (punctured or diluted) vials

- Once a vial has been punctured or diluted (dilution with sodium chloride 9 mg/mL 0.9% solution for injection) chemical and physical in-use stability has been demonstrated for 12 hours at 2 °C to 30 °C.
- From a microbiological point of view, unless the method of opening precludes the risks of microbial contamination, the product should be used immediately after the first puncture of single dose vials and within 12 hours after puncture or dilution of multidose vials. If not used within the recommended duration, in-use storage times and conditions are the responsibility of the user.

Pre-filled syringes

Shelf life of unopened glass pre-filled syringes

12 months when stored at 2 °C to 8 °C.

Verify the storage conditions on the pre-filled syringe label and apply the applicable storage conditions for that presentation.

COMIRNATY glass pre-filled syringes should not be frozen.

Syringes may be stored at temperatures between 8 °C and 30 °C for up to 12 hours.

6.4 Special precautions for storage

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

During use, thawed vials and pre-filled syringes can be handled in room light conditions. Avoid exposure to direct sunlight and ultraviolet light.

6.5 Nature and contents of container

Vials

2 mL clear 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 aluminium seal.

Single dose vial pack size: 10 single dose vials per carton.

Multidose vial pack size: 10 multidose vials per carton.

Pre-filled syringes

Supplied in a single dose glass pre-filled syringe (type I glass syringe) with plunger stopper (synthetic bromobutyl rubber) and a tip cap (synthetic bromobutyl rubber) without needle.

Pack size: 10 pre-filled syringes.

6.6 Special precautions for disposal and other handling

Handling instructions

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

Vials

Handling instructions prior to use

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

Vial Cap and Vial Label Colour	**Time That May Be Required For a 10-vial Pack to Thaw (at 2 °C to 8 °C)**
Light Grey Light Blue Yellow	2 hours
Dark Grey Dark Blue	6 hours

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

Preparation for administration

Vial verification

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

COMIRNATY (Omicron JN.1) (Do Not Dilute) (For 12 Years of Age and Older) (Vials with Grey Cap)
COMIRNATY (Omicron JN.1) (Do Not Dilute) (For Age 5 Years to <12 Years) (Vials with Blue Cap)

INSTRUCTIONS APPLICABLE TO BOTH SINGLE DOSE AND MULTIDOSE VIALS

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

Preparation of individual doses

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

COMIRNATY (Omicron JN.1) (Dilute Before Use) (For Age 6 Months to <5 Years) (Vials with Yellow Cap)

Prior to dilution

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

Dilution instructions

- Thawed vaccine must be diluted in its original vial with sodium chloride 9 mg/mL (0.9%) solution for injection, using a 21 gauge or narrower needle and aseptic techniques. Volume of sodium chloride 9 mg/mL (0.9%) required are noted below:
    - *Yellow cap vials:* 1.1 mL of sodium chloride 9 mg/mL
- Equalise vial pressure before removing the needle from the vial stopper by withdrawing air into the empty diluent syringe. Volume of air required are noted below:
    - *Yellow cap vials:* 1.1 mL of air
- Gently invert the diluted dispersion 10 times. **Do not shake.**
- Check appearance of vaccine after dilution.
    - *Yellow cap vials:* After mixing, the vaccine should present as a clear to slightly opalescent dispersion with no particulates visible. Do not use the vaccine if particulates or discolouration are present.
- After dilution, mark vial with appropriate date/time, store at 2 °C to 30 °C and use within 12 hours. Do not re-freeze.

Preparation of individual doses

- Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
- Withdraw a single dose.
    - *Yellow cap vials (3 doses per vial):* Each dose must contain 0.3 mL of vaccine. Standard syringes can be used.
- If the amount of vaccine remaining in the vial cannot provide a full dose, discard the vial and any excess volume.

Pre-filled syringes

Preparation and administration of individual doses of the refrigerated storage only, glass pre-filled syringes

- Prior to use, the pre-filled syringes can be stored for up to 12 hours at temperatures between 8 °C to 30 °C and can be handled in room light conditions.
- Do not shake.
- Remove tip cap by slowly turning the cap counterclockwise while holding the luer lock.
- Attach a needle appropriate for intramuscular injection and administer the entire volume.

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
www.comirnatyglobal.com	+65 6403 8888

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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