PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

COMIRNATY® Original & Omicron BA.4/BA.5

COVID-19 mRNA vaccine, Bivalent (Original and Omicron BA.4/BA.5)

Suspension for Intramuscular Injection

Multiple Dose Vial

For 12 Years of Age and Older: Gray Cap - DO NOT DILUTE (each vial contains 6[†] doses of 0.3 mL)

Active Immunizing Agent

COMIRNATY® Original & Omicron BA.4/BA.5 [COVID-19 mRNA Vaccine, Bivalent (Original and Omicron B.4/BA.5)] vaccine indicated for:

Active immunization against coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus in individuals 12 years of age and older, has been issued marketing authorization with Terms and Conditions that need to be met by the Market Authorization Holder to ascertain the continued quality, safety and effectiveness of the vaccine.

Patients should be advised of the nature of the authorization. For further information for COMIRNATY® Original & Omicron BA.4/BA.5 [COVID-19 mRNA Vaccine, Bivalent (Original and Omicron BA.4/BA.5)] please refer to Health Canada's COVID-19 vaccines and treatments portal.

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Date of Initial Authorization:
October 7, 2022

Imported and distributed by:
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Submission Control Number: 267502

[†] Low dead-volume syringes and/or needles can be used to extract 6 doses from a single vial. If standard syringes and needles are used, there may not be sufficient volume to extract a 6th dose from a single vial.

RECENT MAJOR LABEL CHANGES

None

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

COMIRNATY Original & Omicron BA.4/BA.5 (COVID-19 mRNA Vaccine, Bivalent (Original and Omicron BA.4/BA.5)) is indicated as a booster dose for active immunization against coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2) in individuals 12 years of age and older (see 4.2 **Recommended Dose and Dosage Adjustment**).

The safety and effectiveness of a booster dose of COMIRNATY Original & Omicron BA.4/BA.5 for individuals 12 years of age and older is inferred from studies of a booster dose of COMIRNATY Original/Omicron BA.1 in individuals >55 years of age and also data from studies of a booster dose of monovalent Omicron BA.1 in individuals 18 to ≤55 years of age.

1.1 Pediatrics

The safety and efficacy of COMIRNATY Original & Omicron BA.4/BA.5 in children under 12 years of age have not yet been established (see **8 ADVERSE REACTIONS** and **14 CLINICAL TRIALS**).

1.2 Geriatrics

Clinical studies of COMIRNATY include participants 65 years of age and older and their data contributes to the overall assessment of safety and efficacy (see **8 ADVERSE REACTIONS** and **14 CLINICAL TRIALS**).

2 CONTRAINDICATIONS

COMIRNATY Original & Omicron BA.4/BA.5 is contraindicated in individuals who are hypersensitive to the active substance or to any ingredient in the formulation. For a complete listing see **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.**

3 SERIOUS WARNINGS AND PRECAUTIONS

At the time of authorization, there are no known serious warnings or precautions associated with this product.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

For 12 Years of Age and Older

COMIRNATY Original & Omicron BA.4/BA.5 is a suspension for intramuscular injection. DO NOT DILUTE (Vials with Gray Cap and Gray Label Border).

A single dose is 0.3 mL.

Dosage Form	Vial Cap and Label Border Colour	Age Range	Dilution Information	Doses Per Vial	Dose Volume
COMIRNATY* Original & Omicron BA.4/BA.5 Multiple Dose Vial **(for 12 years of age and older**: DO NOT DILUTE)	Gray	12 years and older	DO NOT DILUTE prior to use	6	0.3 mL

*May be labeled as Pfizer-BioNTech COVID-19 vaccine

4.2 Recommended Dose and Dosage Adjustment

Booster Dose

A booster dose of COMIRNATY Original & Omicron BA.4/BA.5 may be administered intramuscularly at least 3 to 6 months after completing the primary course of COMIRNATY and/or a previous booster dose of COMIRNATY in individuals 12 years of age or older.

Primary Vaccination Course

COMIRNATY Original & Omicron BA.4/BA.5 is indicated only for booster doses.

For details on the primary vaccination course for individuals 12 years of age and older, please refer to the COMIRNATY® Product Monograph, Section 4.2.1 Vaccination Schedule for Individuals 12 Years of Age and Older.

4.3 Reconstitution

4.3.1 For 12 Years of Age and Older: DO NOT DILUTE (Vials with Gray Cap and Gray Label Border)

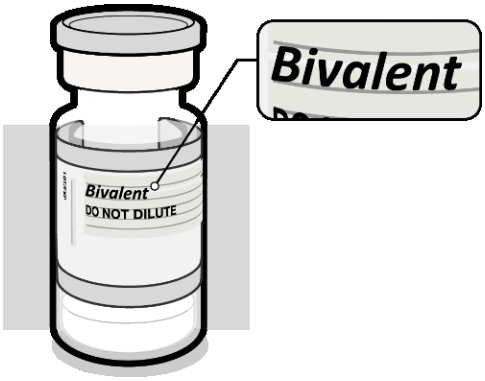
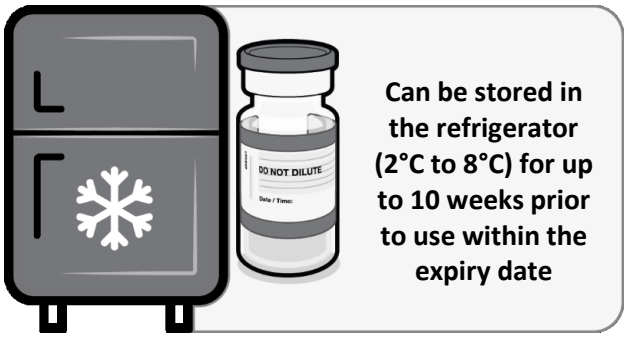
The COMIRNATY Original & Omicron BA.4/BA.5 multiple dose vial with a gray cap and gray label border **MUST NOT BE DILUTED** prior to administration. Instructions on the handling and dose preparation of the vaccine prior to administration are provided below.

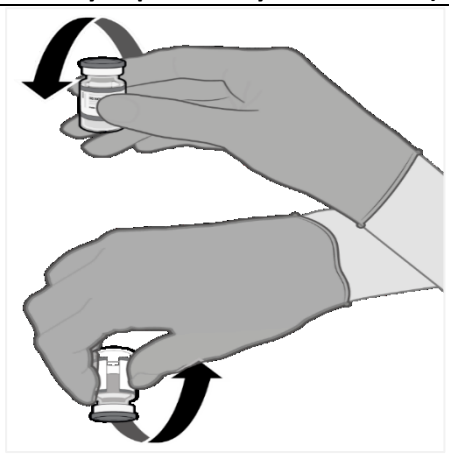
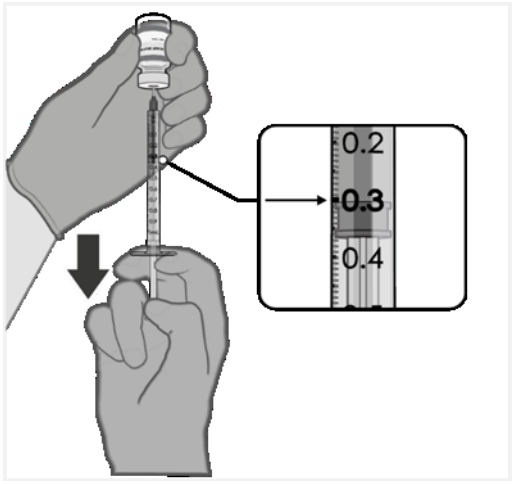
Preparation for Administration

DO NOT DILUTE

- The COMIRNATY Original & Omicron BA.4/BA.5 multiple dose vial with a gray cap and a gray label border contains a volume of 2.25 mL, and is supplied as a frozen suspension that does not contain preservative. Each vial must be thawed prior to administration. **DO NOT DILUTE prior to use.**
- Vials may be thawed in the refrigerator (2°C to 8°C [35°F to 46°F]) or at room temperature (up to 25°C [77°F]) (see **11 STORAGE, STABILITY AND DISPOSAL**).
- The thawed suspension may contain white to off-white opaque amorphous particles.
- One vial contains 6[†] doses of 0.3 mL.
- Refer to thawing and dose preparation instructions in the panels below.

[†] Low dead-volume syringes and/or needles can be used to extract 6 doses from a single vial. If standard syringes and needles are used, there may not be sufficient volume to extract a 6th dose from a single vial.

COMIRNATY Original & Omicron BA.4/BA.5 For 12 Years of Age and Older: DO NOT DILUTE (Vials with Gray Cap and Gray Label Border)	
VIAL AND DOSE VERIFICATION	
 ✓ **Gray plastic cap and label with gray border**	• Verify that the vial: ○ has a gray cap and a label with a gray border **AND** ○ that the product name states that the vaccine is **Bivalent Original & Omicron BA.4/BA.5**. • The date printed on the vial and carton reflects the date of manufacture. The vaccine should not be used after 12 months from the date of manufacture printed on the vial and carton.
THAWING PRIOR TO USE	
	• Thaw vial(s) of COMIRNATY Original & Omicron BA.4/BA.5 before use either by: ○ Allowing vial(s) to thaw in the refrigerator [2°C to 8°C (35°F to 46°F)]. A carton of 10 vials may take up to 6 hours to thaw. ○ Allowing vial(s) to sit at room temperature [up to 25°C (77°F)] for 30 minutes. • Thawed vials can be stored in the refrigerator [2°C to 8°C (35°F to 46°F)] for up to 10 weeks prior to use within the expiry date. • Thawed vials may be stored at room temperature [up to 25°C (77°F)] for up to 12 hours prior to use.

COMIRNATY Original & Omicron BA.4/BA.5 For 12 Years of Age and Older: DO NOT DILUTE (Vials with Gray Cap and Gray Label Border)	
 **Gently × 10**	• Before use, mix by inverting vaccine vial gently 10 times. • Do not shake. • Prior to mixing, the thawed vaccine may contain white to off-white opaque amorphous particles. • After mixing, the vaccine should appear as a white to off-white suspension with no visible particles. • Do not use if liquid is discoloured or if particles are observed after mixing.
PREPARATION OF INDIVIDUAL 0.3 mL DOSES	
 **Withdraw 0.3 mL dose of vaccine**	• Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab, and withdraw 0.3 mL of COMIRNATY Original & Omicron BA.4/BA.5 (for 12 years of age and older) preferentially using a low dead-volume syringe and/or needle. • Each dose must contain 0.3 mL of vaccine. • If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume. • Administer immediately and no later than 12 hours after first puncture. • Low dead-volume syringes and/or needles can be used to extract 6 doses from a single vial. In order to ensure consistent withdrawal of 6 doses of 0.3 mL, it is important to adhere to minimizing volume loss during dose extraction.

COMIRNATY Original & Omicron BA.4/BA.5 For 12 Years of Age and Older: DO NOT DILUTE (Vials with Gray Cap and Gray Label Border)	
 **Record the date and time of first puncture** **Use within 12 hours after first puncture**	• Record the date and time of first vial puncture on the vial label. • Store between 2°C to 25°C (35°F to 77°F). • Discard any unused vaccine 12 hours after first puncture.

4.4 Administration

4.4.1 For 12 Years of Age and Older

Administer a single 0.3 mL dose of COMIRNATY Original & Omicron BA.4/BA.5 intramuscularly, preferably in the deltoid muscle.

Do not inject the vaccine intravascularly, subcutaneously or intradermally.

- DO NOT DILUTE (Vials with Gray Cap and Gray Label Border)
  Vials of COMIRNATY Original & Omicron BA.4/BA.5 with gray caps and gray label borders contain 6 doses of 0.3 mL of vaccine.

Visually inspect each dose in the dosing syringe prior to administration. The vaccine will be an off-white suspension. During the visual inspection:

- Verify the final dosing volume of 0.3 mL.
- Confirm there are no particulates and that no discolouration is observed.
- Do not administer if vaccine is discoloured or contains particulate matter.

Low dead-volume syringes and/or needles can be used to extract 6 doses from a single vial. In order to ensure consistent withdrawal of 6 doses of 0.3 mL, it is important to adhere to minimizing volume loss during dose extraction. **If standard syringes and needles are used, there may not be sufficient volume to extract a 6th dose from a single vial.** Irrespective of the type of syringe and needle:

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

5 OVERDOSAGE

In the event of suspected overdose, monitoring of vital functions and symptomatic treatment is recommended. Contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of vaccines for patient immunization record-keeping as well as safety monitoring, health professionals should record the time and date of administration, quantity of administered dose (if applicable), anatomical site and route of administration, brand name and generic name of the vaccine, the product lot number and expiry date (or manufacture date).

For 12 Years of Age and Older: DO NOT DILUTE (Vials with Gray Cap and Gray Label Border)

COMIRNATY Original & Omicron BA.4/BA.5 is supplied as a frozen suspension in multiple dose vials with gray caps and labels with gray borders. **Do not dilute.** Each vial contains 6[†] doses of 0.3 mL. Each 0.3 mL dose of COMIRNATY Original & Omicron BA.4/BA.5 contains 15 mcg of a nucleoside modified messenger RNA (modRNA) encoding the viral spike (S) glycoprotein of SARS-CoV-2 original strain and 15 mcg of modRNA encoding the S glycoprotein of SARS-CoV-2 Omicron variant lineages BA.4 and BA.5 (Omicron BA.4/BA.5). Each dose contains 30 mcg modRNA in total and also includes the non-medicinal ingredients listed in Table 1.

COMIRNATY Original & Omicron BA.4/BA.5 does not contain preservative. The vial stoppers are not made with natural rubber latex.

COMIRNATY Original & Omicron BA.4/BA.5 multiple dose vials (with gray cap and gray label border) are supplied in a carton containing 10 multiple dose vials.

Table 1: Dosage Forms, Strengths, Composition and Packaging (For 12 Years of Age and Older)

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intramuscular injection	**DO NOT DILUTE (Vials with Gray Cap and Gray Label Border)** Suspension (do not dilute) Tozinameran (mRNA) encodes for the viral spike (S) protein of SARS-CoV-2 Original strain and famtozinameran (mRNA) encodes for the viral spike (S) protein of SARS-CoV-2 Omicron BA.4/BA.5 strain Multiple dose vial (each vial contains 6[†] doses of 0.3 mL)	• ALC-0315 = ((4-hydroxybutyl) azanediyl)bis (hexane-6,1-diyl)bis(2-hexyldecanoate) • ALC-0159 = 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide • 1,2-distearoyl-sn-glycero-3-phosphocholine • cholesterol • sodium chloride • sucrose • tromethamine • tromethamine hydrochloride • water for injection

[†] Low dead-volume syringes and/or needles can be used to extract 6 doses from a single vial. If standard syringes and needles are used, there may not be sufficient volume to extract a 6[th] dose from a single vial.

7 WARNINGS AND PRECAUTIONS

General

The administration of COMIRNATY Original & Omicron BA.4/BA.5 should be postponed in individuals suffering from acute severe febrile illness.

Fainting may occur in association with administration of injectable vaccines. Individuals should be advised to bring symptoms (e.g., dizziness, increases in heart rate, feeling short of breath, tingling sensations or sweating) to the attention of the vaccination provider for evaluation. Procedures should be in place to avoid injury from fainting.

As with any vaccine, vaccination with COMIRNATY Original & Omicron BA.4/BA.5 may not protect all recipients.

Acute Allergic Reactions

Anaphylaxis has been reported. As with all vaccines, training for immunizers, appropriate medical treatment and supervision after immunization should always be readily available in case of a rare anaphylactic event following the administration of this vaccine.

Vaccine recipients should be kept under observation for at least 15 minutes after immunization; 30 minutes is a preferred interval when there is a specific concern about a possible vaccine reaction.

COMIRNATY Original & Omicron BA.4/BA.5 should not be given to those who have experienced anaphylaxis after a prior dose of COMIRNATY, COMIRNATY Original/Omicron BA.1, or COMIRNATY Original & Omicron BA.4/BA.5.

Cardiovascular

Myocarditis and Pericarditis

Very rare cases of myocarditis and/or pericarditis following vaccination with COMIRNATY have been reported during post-authorization use. These cases occurred more commonly after the second dose and in adolescents and young adults. Typically, the onset of symptoms has been within a few days following receipt of COMIRNATY. Available short-term follow-up data suggest that the symptoms resolve in most individuals, but information on long-term sequelae is lacking. The decision to administer COMIRNATY Original & Omicron BA.4/BA.5 to an individual with a history of myocarditis or pericarditis should take into account the individual's clinical circumstances.

Healthcare professionals are advised to consider the possibility of myocarditis and/or pericarditis in their differential diagnosis if individuals present with chest pain, shortness of breath, palpitations or other signs and symptoms of myocarditis and/or pericarditis following immunization with a COVID-19 vaccine. This could allow for early diagnosis and treatment. Cardiology consultation for management and follow up should be considered.

Driving and Operating Machinery

COMIRNATY Original & Omicron BA.4/BA.5 has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under **8 ADVERSE REACTIONS** may temporarily affect the ability to drive or use machines.

Fertility

It is unknown whether this vaccine has an impact on fertility. Animal studies do not indicate direct or indirect harmful effects with respect to female fertility or reproductive toxicity (see **16 NON-CLINICAL TOXICOLOGY**).

Hematologic

Individuals receiving anticoagulant therapy or those with a bleeding disorder that would contraindicate intramuscular injection should not be given the vaccine unless the potential benefit clearly outweighs the risk of administration.

Immune

The efficacy and safety of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to the vaccine.

7.1 Special Populations

7.1.1 Pregnant Women

No data are available yet regarding the use of COMIRNATY Original & Omicron BA.4/BA.5 during pregnancy.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/ fetal development, parturition, or post-natal development (see **16 NON-CLINICAL TOXICOLOGY**).

7.1.2 Breast-feeding

No data are available yet regarding the use of COMIRNATY Original & Omicron BA.4/BA.5 during breast- feeding.

It is unknown whether COMIRNATY Original & Omicron BA.4/BA.5 is excreted in human milk. A risk to the newborns/infants cannot be excluded.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for immunization against COVID-19.

7.1.3 Pediatrics

The safety and efficacy of COMIRNATY Original & Omicron BA.4./BA.5 in children under 12 years of age have not yet been established.

7.1.4 Geriatrics

Clinical studies of COMIRNATY Original/Omicron BA.1 include participants 65 years of age and older, who received the primary series and a booster dose of COMIRNATY, and their data contributes to the overall assessment of safety and efficacy (See **8 ADVERSE REACTIONS** and **14 CLINICAL TRIALS**).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

8.1.1 COMIRNATY Original & Omicron BA.4/BA.5

The safety of a booster dose of COMIRNATY Original & Omicron BA.4/BA.5 for individuals 12 years of age and older is inferred from safety data from studies of a booster dose of COMIRNATY Original/Omicron BA.1 in individuals >55 years of age and also safety data from studies of a booster dose of monovalent Omicron BA.1 in individuals 18 to ≤55 years of age.

The safety of a booster dose of COMIRNATY Original & Omicron BA.4/BA.5 is also based on:

- safety data from clinical trials which evaluated primary and booster vaccination with COMIRNATY (see **8.2 Clinical Trial Adverse Reactions**) and
- post marketing safety data with COMIRNATY.

Safety data accrued with the COMIRNATY Original/Omicron BA.1 vaccine and with COMIRNATY are relevant to the COMIRNATY Original & Omicron BA.4/BA.5 vaccine because these vaccines are manufactured using the same process.

Participants >55 Years of Age – After a Dose of COMIRNATY Original/Omicron BA.1 as a Second Booster (4th Dose)

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

The overall safety profile for the COMIRNATY Original/Omicron BA.1 booster (Dose 4) was similar to that seen after the COMIRNATY booster (Dose 3). The most frequent adverse reactions in participants >55 years of age were pain at the injection site (58.1%), fatigue (49.2%), headache (33.6%), myalgia (22.3%), chills (13.0%) and arthralgia (11.3%). No new adverse reactions were identified for COMIRNATY Original/Omicron BA.1.

Participants 18 to ≤ 55 Years of Age – After a Booster Dose of Monovalent Omicron BA.1

The safety of a COMIRNATY Original/Omicron BA.1 booster dose in individuals 18 - ≤ 55 years of age is extrapolated from safety data from a subset of 315 adults 18 - ≤55 years of age who received a booster (Dose 4) of Omicron BA.1 30 mcg (monovalent) after completing 3 doses of COMIRNATY. The most frequent adverse reactions in these participants 18 - ≤55 years of age were pain at the injection site (77.9%), fatigue (64.3%), headache (47.6%), myalgia (33.7%), chills (31.6%) and arthralgia (23.5%).

8.1.2 COMIRNATY (30 mcg)

Study BNT162-01 (Study 1) was a Phase 1/2, two-part dose-escalation trial that enrolled 60 participants 18 through 55 years of age and 36 participants 56 through 85 years of age.

Study C4591001 (Study 2) is a Phase 1/2/3, multicenter, multinational, randomized, saline placebo-controlled, observer-blind, dose-finding, vaccine candidate-selection (Phase 1) and efficacy (Phase 2/3) study that has enrolled approximately 46,000 participants, 12 years of age or older. Of these,

approximately 44,047 participants (22,026 COMIRNATY; 22,021 placebo) in Phase 2/3 are 16 years of age or older (including 378 and 376 adolescents 16 and 17 years of age in the vaccine and placebo groups, respectively) and 2,260 adolescents are 12 to 15 years of age (1,131 and 1,129 in the vaccine and placebo groups, respectively). Of the total number of COMIRNATY recipients in the study, 20.7% were 65 years of age and older. Study 2 also included 200 participants with confirmed stable human immunodeficiency virus (HIV) infection. HIV-positive participants are included in safety population disposition but are summarized separately in safety analyses.

Additionally, 306 existing Phase 3 participants 18 through 55 years of age received a booster dose of COMIRNATY approximately 6 months (range of 4.8 to 8.0 months) after completing 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 at least 6 months after the second dose. The overall safety profile for the booster dose was similar to that seen after 2 doses.

The safety evaluation of participants in Study 2 and Study 4 is ongoing. In Study 2, all participants 12 to 15 years of age and 16 years of age and older in the reactogenicity subset, and a subset of 306 participants 18 through 55 years of age who received a booster dose in Study 2, were monitored for solicited local and systemic reactions and use of antipyretic medication after each vaccination with an electronic diary during the 7 days following any dose of vaccination. Participants, including those who received a booster in Study 4, continue to be monitored for unsolicited adverse events (AEs), including serious adverse events (SAEs), throughout the study [from Dose 1 to 1 month after the last dose (all AEs) and 6 months (SAEs) after the last vaccination].

Participants 12 Years of Age and Older

At the time of the analysis of Study 2 (data accrued through March 13, 2021), a total of 25,651 (58.2%) participants (13,031 in vaccine group and 12,620 in placebo group) 16 years of age and older had been followed up for at least 4 months, with 3,082 (7.0%) participants (1,778 in vaccine group and 1,304 in placebo group) followed up for at least 6 months after the second dose during the blinded placebo-controlled follow-up period. A total of 12,006 (54.5%) participants originally randomized to the vaccine group in Study 2 had been followed up for at least 6 months after the second dose including the blinded and open-label periods.

In an analysis of Study 2, based on data up to the cut-off date of March 13, 2021, a total of 2,260 adolescents (1,131 COMIRNATY; 1,129 placebo) were 12 to 15 years of age. Of these,1,559 (786 COMIRNATY and 773 placebo) adolescents have been followed for ≥4 months after the second dose of COMIRNATY.

In clinical studies with a data cut-off of March 13, 2021, and where 2 doses were administered 3 weeks apart, the most common adverse reactions in the reactogenicity subset (n=4,924) of participants 16 years of age and older after any dose included injection site pain (84.3%), fatigue (64.7%), headache (57.1%), muscle pain (40.2%), chills (34.7%), joint pain (25.0%), fever (15.2%), injection site swelling (11.1%), and injection site redness (9.9%). Additional AEs reported in the safety population (n=21,926) of participants 16 years of age and older from dose 1 to 1 month after dose 2 included nausea (1.2%), malaise (0.6%), lymphadenopathy (0.4%), asthenia (0.3%), decreased appetite (0.2%), hyperhidrosis (0.1%), lethargy (0.1%), and night sweats (0.1%). Adverse reactions were usually mild or moderate in intensity and resolved within a few days after vaccination.

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

In a clinical study with a data cut-off date of 02 September 2021, the most commonly reported (≥8%) adverse reactions in adolescents 12 through 15 years of age following any dose were pain at the injection site (90.5%), fatigue (77.5%), headache (75.5%), chills (49.2%), muscle pain (42.2%), fever (24.3%), joint pain (20.2%), injection site swelling (9.2%), and injection site redness (8.6%).

In a clinical study of participants 18 through 55 years of age (N=306), 289 participants (94%) completed the e-diary recording adverse reactions. The most commonly reported adverse reactions (≥10%) following administration of a booster dose were pain at the injection site (83.0%), fatigue (63.7%), headache (48.4%), muscle pain (39.1%), chills (29.1%), and joint pain (25.3%).

In a clinical study of approximately 10,000 participants 16 years of age and older, unsolicited adverse reactions following administration of a booster dose included headache (5%), fever (4.8%), lymphadenopathy (2.8%), pain in extremity (1.1%), nausea (0.9%), malaise (0.7%), and decreased appetite (0.2%).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials, therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

8.2.1 COMIRNATY Original/Omicron BA.1 (15/15 mcg)

Solicited Local Adverse Reactions (AR)s

Pain at injection site was the most frequently reported local AR within 7 days after study vaccination, with swelling and redness at the injection site reported much less frequently. Local ARs are summarized in Table 2.

Table 2: Solicited Local Adverse Reactions Reported for Vaccine Groups Within 7 Days After Study Vaccination

Local Reaction	COMIRNATY 30 mcg (N=298)	COMIRNATY Original/Omicron 30 mcg (N=301)
Pain at injection site	60.1%	58.1%
Redness at injection site	6.4%	7.0%
Swelling at injection site	6.0%	6.6%

Most solicited local ARs were mild or moderate in severity. Severe local ARs were reported infrequently in both vaccine groups; severe events after study vaccination included injection site pain (0.3%), swelling (0.2%) and redness (0.3%). No Grade 4 local reactions were reported in either vaccine group evaluated. The median onset for all local reactions across vaccine groups evaluated was 2 days, and all events resolved within a median duration of 1 to 2 days after onset.

Solicited Systemic Adverse Reactions (ARs)

Fatigue was the most frequently reported systemic AR reported within 7 days after study vaccination,

followed by headache, and less frequently chills, muscle and joint pain. Vomiting, diarrhea and fever were the least frequently reported systemic events and occurred at similar frequencies across vaccine groups. Fever >38.9 °C to 40.0 °C was reported by 4 participants in the COMIRNATY Original/BA.1 30 mcg group and 0 participants in the COMIRNATY 30 mcg group.

Most frequently reported systemic events in decreasing order of frequency after study vaccination (Table 3) were:

Table 3: Solicited Systemic Adverse Reactions Reported for Vaccine Groups Within 7 Days After Study Vaccination

Systemic Reaction	COMIRNATY 30 mcg (N=298)	COMIRNATY Original/Omicron 30 mcg (N=301)
Fatigue	45.3%	49.2%
Headache	26.5%	33.6%
Muscle pain	19.8%	22.3%
Chills	16.4%	13.0%
Joint pain	9.1%	11.3%
Diarrhea	4.4%	9.0%
Fever (≥38.0°C)	3.7%	5.0%
Vomiting	1.3%	1.7%

Most systemic events were mild or moderate in severity. Severe systemic events were reported infrequently in both vaccine groups. No Grade 4 systemic events were reported in any vaccine groups evaluated. The median onset for all systemic events across both vaccine groups evaluated was 2 to 3 days and all events resolved within a median duration of 1 to 2 days after onset.

Overview of Adverse Events (AEs) – From Study Vaccination to 1 Month Post-Dose

In total, 5.9% and 6.2% of participants reported any AE (with 0% and 0.3% reporting any serious AE) from study vaccination through 1 month post-dose in the COMIRNATY (30 mcg) and COMIRNATY Original/Omicron BA.1 (30 mcg), respectively. No withdrawals due to AEs or deaths were reported.

Overall, the AE profiles after study vaccination (Dose 4) with COMIRNATY (30 mcg) or COMIRNATY Original/BA.1 (30 mcg) reflected mostly reactogenicity events and did not suggest any clinically important short-term safety concerns.

Adverse Events (AEs) from Study Vaccination to Data Cut-off Date

From study vaccination to the data cut-off date (16 May 2022), the proportions of participants with any AEs were generally similar. As of the data cut-off date, any related or any severe AEs were reported across the vaccine groups by ≤5.1% or ≤0.9% of participants, respectively.

Few additional AEs were reported from study vaccination from post-dose to the data cut-off date for participants in the COMIRNATY 30 mcg (6.6% vs 5.9%) group. Two additional severe AEs, also reported as SAEs (pneumonia, ischaemic stroke) were reported in the COMIRNATY 30 mcg group. No withdrawals due to AEs were reported in any of the groups beyond 1-month post-dose. No study participants died.

Overall, frequencies of any AEs reported after study vaccination up to the data cut-off date were generally similar between both vaccine groups. Many of the AEs were consistent with reactogenicity events (e.g., fever and fatigue). Most of the additional AEs reported after 1 month post-dose up to the data cut-off date consisted of unrelated events such as spinal osteoarthritis, ischaemic stroke, breast tenderness and tooth extraction. Additional analyses of AEs from post-dose to the data cut-off did not suggest any meaningful differences in the safety profile.

8.2.2 COMIRNATY (30 mcg)

Participants 16 Years of Age and Older – Primary Series (Two Doses)

Solicited Adverse Reactions

Tables 4 through 7 present the frequency and severity of solicited local and systemic reactions, respectively, within 7 days following each dose of COMIRNATY and placebo in the subset of participants 16 years of age and older (n=9,839) in the safety population who were monitored for reactogenicity with an electronic diary.

Table 4: Study 2 – Frequency of Solicited Local Reactions Within 7 Days After Each Dose of COMIRNATY– Participants 16-55 Years of Age (Reactogenicity Subset of the Safety Population*)

Local Reaction	Dose 1		Dose 2	
	COMIRNATY N[a]=2,899 n[b] (%)	Placebo N[a]=2,908 n[b] (%)	COMIRNATY N[a]=2,682 n[b] (%)	Placebo N[a]=2,684 n[b] (%)
Redness				
Any[c]	156 (5.4)	28 (1.0)	151 (5.6)	18 (0.7)
Severe[d]	7 (0.2)	3 (0.1)	11 (0.4)	0 (0.0)
Swelling				
Any[c]	184 (6.3)	16 (0.6)	183 (6.8)	5 (0.2)
Severe[d]	6 (0.2)	2 (0.1)	7 (0.3)	0 (0.0)
Pain at the injection site				
Any[c]	2,426 (83.7)	414 (14.2)	2,101 (78.3)	312 (11.6)
Severe[e]	39 (1.3)	3 (0.1)	39 (1.5)	0 (0.0)
Any local reaction[c]	2,444 (84.3)	432 (14.9)	2,108 (78.6)	325 (12.1)

*Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.
a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose. No Grade 4 solicited local reactions were reported in participants 16-55 years of age.
b. n = Number of participants with the specified reaction.
c. Any local reaction: any redness >2.0 cm, any swelling >2.0 cm, or any pain at the injection site.
d. Severe: >10.0 cm.
e. Severe: prevents daily activity.

Table 5: Study 2 – Frequency of Solicited Systemic Reactions Within 7 Days After Each Dose of COMIRNATY – Participants 16-55 Years of Age (Reactogenicity Subset of the Safety Population*)

Systemic Reaction	Dose 1		Dose 2	
	COMIRNATY N[a]=2,899 n[b] (%)	Placebo N[a]=2,908 n[b] (%)	COMIRNATY N[a]=2,682 n[b] (%)	Placebo N[a]=2,684 n[b] (%)
Fever				
≥38.0°C	119 (4.1)	25 (0.9)	440 (16.4)	11 (0.4)
>38.9°C	8 (0.3)	4 (0.1)	40 (1.5)	2 (0.1)
Fatigue				
Any	1,431 (49.4)	960 (33.0)	1,649 (61.5)	614 (22.9)
Severe[d]	41 (1.4)	18 (0.6)	142 (5.3)	14 (0.5)
Headache				
Any	1,262 (43.5)	975 (33.5)	1,448 (54.0)	652 (24.3)
Severe[d]	33 (1.1)	24 (0.8)	91 (3.4)	18 (0.7)
Chills				
Any	479 (16.5)	199 (6.8)	1,015 (37.8)	114 (4.2)
Severe[d]	15 (0.5)	2 (0.1)	69 (2.6)	2 (0.1)
Vomiting				
Any	34 (1.2)	36 (1.2)	58 (2.2)	30 (1.1)
Severe[e]	0 (0.0)	1 (0.0)	4 (0.1)	0 (0.0)
Diarrhea				
Any	309 (10.7)	323 (11.1)	269 (10.0)	205 (7.6)
Severe[f]	3 (0.1)	1 (0.0)	6 (0.2)	1 (0.0)
New or worsened muscle pain				
Any	664 (22.9)	329 (11.3)	1,055 (39.3)	237 (8.8)
Severe[d]	15 (0.5)	2 (0.1)	62 (2.3)	3 (0.1)
New or worsened joint pain				
Any	342 (11.8)	168 (5.8)	638 (23.8)	147 (5.5)
Severe[d]	5 (0.2)	1 (0.0)	27 (1.0)	4 (0.1)
Any systemic reaction[c]	1,979 (68.3)	1,559 (53.6)	2,034 (75.8)	1,026 (38.2)
Use of antipyretic or pain medication	805 (27.8)	398 (13.7)	1213 (45.2)	320 (11.9)

*Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.
a. N =Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose. No Grade 4 solicited systemic reactions were reported in participants 16-55 years of age.
b. n = Number of participants with the specified reaction.
c. Any systemic reaction: any fever ≥38.0°C, any fatigue, any vomiting, any chills, any diarrhea, any headache, any new or worsened muscle pain, or any new or worsened joint pain.
d. Severe: prevents daily activity.
e. Severe: requires intravenous hydration.
f. Severe: 6 or more loose stools in 24 hours.

Table 6: Study 2 – Frequency of Solicited Local Reactions Within 7 Days After Each Dose of COMIRNATY – Participants 56 Years of Age and Older (Reactogenicity Subset of the Safety Population*)

Local Reaction	Dose 1		Dose 2	
	COMIRNATY N[a]=2,008 n[b] (%)	**Placebo N[a]=1,989 n[b] (%)**	**COMIRNATY N[a]=1,860 n[b] (%)**	**Placebo N[a]=1,833 n[b] (%)**
Redness				
Any[c]	106 (5.3)	20 (1.0)	133 (7.2)	14 (0.8)
Severe[d]	5 (0.2)	2 (0.1)	10 (0.5)	1 (0.1)
Swelling				
Any[c]	141 (7.0)	23 (1.2)	145 (7.8)	13 (0.7)
Severe[d]	2 (0.1)	0 (0.0)	4 (0.2)	1 (0.1)
Pain at the injection site				
Any[c]	1,408 (70.1)	185 (9.3)	1,230 (66.1)	143 (7.8)
Severe[e]	4 (0.2)	0 (0.0)	10 (0.5)	0 (0.0)
Any local reaction[c]	1,433 (71.4)	207 (10.4)	1243 (66.8)	158 (8.6)

*Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.
a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose. No Grade 4 solicited local reactions were reported in participants 56 years of age and older.
b. n = Number of participants with the specified reaction.
c. Any local reaction: any redness >2.0 cm, any swelling >2.0 cm, or any pain at the injection site.
d. Severe: >10.0 cm.
e. Severe: prevents daily activity.

Table 7: Study 2 – Frequency of Solicited Systemic Reactions Within 7 Days After Each Dose of COMIRNATY – Participants 56 Years of Age and Older (Reactogenicity Subset of the Safety Population*)

Systemic Reaction	Dose 1		Dose 2	
	COMIRNATY N[a]=2,008 n[b] (%)	Placebo N[a]=1,989 n[b] (%)	COMIRNATY N[a]=1,860 n[b] (%)	Placebo N[a]=1,833 n[b] (%)
Fever				
≥38.0°C	26 (1.3)	8 (0.4)	219 (11.8)	4 (0.2)
>38.9°C	1 (0.0)	2 (0.1)	7 (0.4)	1 (0.1)
Fatigue				
Any	677 (33.7)	447 (22.5)	949 (51.0)	306 (16.7)
Severe[d]	3 (0.1)	3 (0.2)	60 (3.2)	2 (0.1)
Grade 4[g]	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Headache				
Any	503 (25.0)	363 (18.3)	733 (39.4)	259 (14.1)
Severe[d]	2 (0.1)	3 (0.2)	13 (0.7)	5 (0.3)
Chills				
Any	130 (6.5)	69 (3.5)	435 (23.4)	57 (3.1)
Severe[d]	0 (0.0)	1 (0.1)	21 (1.1)	0 (0.0)
Vomiting				
Any	10 (0.5)	9 (0.5)	13 (0.7)	5 (0.3)
Severe[e]	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Diarrhea				
Any	168 (8.4)	130 (6.5)	152 (8.2)	102 (5.6)
Severe[f]	4 (0.2)	1 (0.1)	2 (0.1)	4 (0.2)
New or worsened muscle pain				
Any	274 (13.6)	165 (8.3)	537 (28.9)	99 (5.4)
Severe[d]	1 (0.0)	3 (0.2)	20 (1.1)	1 (0.1)
New or worsened joint pain				
Any	175 (8.7)	124 (6.2)	353 (19.0)	72 (3.9)
Severe[d]	3 (0.1)	1 (0.1)	9 (0.5)	1 (0.1)
Any systemic reaction[c]	984 (49.0)	749 (37.7)	1,203 (64.7)	516 (28.2)
Use of antipyretic or pain medication	382 (19.0)	224 (11.3)	688 (37.0)	170 (9.3)

*Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.
a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose. The only Grade 4 solicited systemic reaction reported in participants 56 years of age and older was fatigue.
b. n = Number of participants with the specified reaction.
c. Any systemic reaction: any fever ≥38.0°C, any fatigue, any vomiting, any chills, any diarrhea, any headache, any new or worsened muscle pain, or any new or worsened joint pain.
d. Severe: prevents daily activity.
e. Severe: requires intravenous hydration.
f. Severe: 6 or more loose stools in 24 hours.
g. Grade 4: emergency room visit or hospitalization.

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

Unsolicited Adverse Events

The participants were unblinded to offer placebo participants COMIRNATY when they became locally eligible under regulatory approval in December 2020. A total of 25,651 (58.2%) participants (13,031 in vaccine group and 12,620 in placebo group) 16 years of age and older had been followed up for at least 4 months, with 3,082 (7.0%) participants (1,778 in vaccine group and 1,304 in placebo group) followed up for at least 6 months after the second dose during the blinded placebo-controlled follow-up period in Study 2. Adverse events detailed below for participants 16 years of age and older are for the placebo-controlled blinded follow-up period up to the participants' unblinding dates.

Among participants 16 through 55 years of age who received at least one dose of study vaccine, 12,995 of whom received COMIRNATY and 13,026 of whom received placebo, unsolicited adverse events were reported by 4,396 (33.8%) participants in the COMIRNATY group and 2,136 (16.4%) participants in the placebo group. In a similar analysis in participants 56 years of age and older that included 8,931 COMIRNATY recipients and 8,895 placebo recipients, unsolicited adverse events were reported by 2,551 (28.6%) participants in the COMIRNATY group and 1,432 (16.1%) participants in the placebo group. Among participants with confirmed stable HIV infection that included 100 COMIRNATY recipients and 100 placebo recipients, unsolicited adverse events were reported by 29 (29%) participants in the COMIRNATY group and 15 (15%) participants in the placebo group.

Lymphadenopathy was reported in 87 (0.4%) participants in the vaccine group compared to 8 (<0.1%) participants in the placebo group. Bell's palsy (facial paralysis and facial paresis) was reported by four participants in the vaccine group and two in the placebo group. In the four vaccinated participants, events began from 3 to 48 days after their last dose, were mild to moderate in severity, and duration ranged from 3 to 68 days. Currently available information is insufficient to determine a causal relationship with the vaccine. There were no other notable patterns or numerical imbalances between treatment groups for specific categories of non-serious adverse events (including other neurologic or neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to COMIRNATY. Cumulative safety follow-up to at least 6 months after Dose 2 for approximately 12,000 participants who received COMIRNATY showed no other safety signals arising from longer-term follow-up of the study.

Serious Adverse Events

In Study 2, among participants 16 through 55 years of age who had received at least 1 dose of vaccine or placebo (COMIRNATY = 12,995; placebo = 13,026), serious adverse events from Dose 1 up to the participant unblinding date in ongoing follow-up were reported by 103 (0.8%) COMIRNATY recipients and 117 (0.9%) placebo recipients. In a similar analysis, in participants 56 years of age and older (COMIRNATY = 8,931; placebo = 8,895), serious adverse events were reported by 165 (1.8%) COMIRNATY recipients and 151 (1.7%) placebo recipients who received at least 1 dose of COMIRNATY or placebo, respectively. Among participants with confirmed stable HIV infection serious adverse events from Dose 1 up to the participant unblinding date in ongoing follow-up were reported by 2 (2%) COMIRNATY recipients and 2 (2%) placebo recipients.

Pericarditis was reported for one participant in the vaccine group, and no case was reported in the placebo group. Appendicitis was reported as a serious adverse event for 27 participants, 15 vaccine participants and 12 placebo participants. Currently available information is insufficient to determine a

causal relationship with the vaccine. There were no other notable patterns or numerical imbalances between treatment groups for specific categories of serious adverse events (including neurologic, neuro-inflammatory, thrombotic events, myocarditis or anaphylactic reaction to the vaccine) reported during the blinded placebo-controlled follow-up period of the study.

Participants 16 Years of Age and Older – After Booster Dose

A subset from Study C4591001 (Study 2) Phase 2/3 participants, of 306 adults 18 through 55 years of age who completed the original COMIRNATY 2-dose series, received a booster dose of COMIRNATY approximately 6 months (range of 4.8 to 8.0 months) after receiving Dose 2.

In Study C4591031 (Study 4), a placebo-controlled booster study, participants 16 years of age and older recruited from Study C4591001 (Study 2) received a booster dose of COMIRNATY (5,081 participants), or placebo (5,044 participants) at least 6 months after the second dose of COMIRNATY. Overall, participants who received a booster dose, had a median follow-up time of 2.5 months after the booster dose to the cut-off date (5 October 2021). Among the participants, the median age was 53.0 years (range 16 through 87 years of age), including 1,175 booster dose recipients (23.1%) who were ≥65 years of age, 49.1% were male and 50.9% were female, 79.0% were White, 14.9% were Hispanic/Latino, 9.2% were Black or African American, 5.5% were Asian, and 1.7% were American Indian/Alaska Native.

Solicited Local and Systemic Adverse Reactions

Overall, among participants who received a booster dose in a subset from Study C4591001 (Study 2), the median age was 42 years (range 19 through 55 years of age), 45.8% were male and 54.2% were female, 81.4% were White, 27.8% were Hispanic/Latino, 9.2% were Black or African American, 5.2% were Asian, and 0.7% were American Indian/Alaska Native.

Table 8: Study 2 – Frequency and Percentages of Participants With Solicited Local Reactions, By Maximum Severity, Within 7 Days After the Booster Dose of COMIRNATY – Booster Dose Safety Population*

Solicited Local Reaction	**COMIRNATY Booster Dose N[a] = 289 n[b] (%)**
Redness[c]	
Any (>2 cm)	17 (5.9)
Severe	0
Swelling[c]	
Any (>2 cm)	23 (8.0)
Severe	1 (0.3)
Pain at the injection site[d]	
Any	240 (83.0)
Severe	1 (0.3)

Note: Reactions were collected in the electronic diary (e-diary) from Day 1 to Day 7 after the booster dose.
Note: No Grade 4 solicited local reactions were reported.
*Participants in the safety analysis population who received the booster dose of COMIRNATY.
a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.
b. n = Number of participants with the specified reaction.
c. Mild: >2.0 to 5.0 cm; Moderate: >5.0 to 10.0 cm; Severe: >10.0 cm.
d. Mild: does not interfere with activity; Moderate: interferes with activity; Severe: prevents daily activity.

In participants who received a booster dose the mean duration of pain at the injection site after the booster dose was 2.6 days (range 1 to 8 days), for redness 2.2 days (range 1 to 15 days), and for swelling 2.2 days (range 1 to 8 days).

Table 9: Study 2 – Frequency and Percentages of Participants With Solicited Systemic Reactions, by Maximum Severity, Within 7 Days After the Booster Dose of COMIRNATY – Booster Dose Safety Population*

Solicited Systemic Reaction	COMIRNATY Booster Dose N[a] = 289 n[b] (%)
Fever	
≥38.0°C	25 (8.7)
≥38.0°C to 38.4°C	12 (4.2)
>38.4°C to 38.9°C	12 (4.2)
>38.9°C to 40.0°C	1 (0.3)
>40.0°C	0
Fatigue[c]	
Any	184 (63.7)
Severe	13 (4.5)
Headache[c]	
Any	140 (48.4)
Severe	3 (1.0)
Chills[c]	
Any	84 (29.1)
Severe	3 (1.0)
Vomiting[d]	
Any	5 (1.7)
Severe	0
Diarrhea[e]	
Any	25 (8.7)
Severe	0
New or worsened muscle pain[c]	
Any	113 (39.1)
Severe	4 (1.4)
New or worsened joint pain[c]	
Any	73 (25.3)
Severe	1 (0.3)
Use of antipyretic or pain medication[f]	135 (46.7)

Note: Events and use of antipyretic or pain medication were collected in the electronic diary (e-diary) from Day 1 to Day 7 after the booster dose.
Note: No Grade 4 solicited systemic reactions were reported.
*Randomized participants in the safety analysis population who received the booster dose of COMIRNATY.
a. N = Number of participants reporting at least 1 yes or no response for the specified event after the specified dose.
b. n = Number of participants with the specified reaction.
c. Mild: does not interfere with activity; Moderate: some interference with activity; Severe: prevents daily activity.
d. Mild: 1 to 2 times in 24 hours; Moderate: >2 times in 24 hours; Severe: requires intravenous hydration.

e. Mild: 2 to 3 loose stools in 24 hours; Moderate: 4 to 5 loose stools in 24 hours; Severe: 6 or more loose stools in 24 hours.
f. Severity was not collected for use of antipyretic or pain medication.

Unsolicited Adverse Events

Overall, participants who received a booster dose in Study C4591031 (Study 4), had a median follow-up time of 2.5 months after the booster dose to the cut-off date (October 5, 2021).

In an analysis of all unsolicited adverse events reported following the booster dose of COMIRNATY, through 1 month after the booster dose, in participants 16 through 87 years of age (N = 5,055), adverse reactions included headache (5%), fever (4.8%), lymphadenopathy (2.8%), decreased appetite (0.2%), malaise (0.7%), nausea (0.9%), and pain in extremity (1.1%).

Serious Adverse Events

Of the participants who received a booster dose of COMIRNATY or placebo (COMIRNATY = 5,055; placebo = 5,020) to the cut-off date (October 5, 2021), serious adverse events were reported by 0.3% of COMIRNATY recipients and 0.5% by placebo recipients. There were no notable patterns or numerical imbalances between treatment groups for specific categories of serious adverse events that would suggest a causal relationship to COMIRNATY. A 17-year-old male in Study 2 was diagnosed with myocarditis three days after receiving the booster dose (Dose 3). The participant was treated and recovered.

Adolescents 12 to 15 Years of Age – Primary Series (Two Doses)

Solicited Adverse Reactions

Table 10 and Table 11 present the frequency and severity of solicited local and systemic reactions, respectively, within 7 days following each dose of COMIRNATY and placebo in adolescents 12 to 15 years of age included in the safety population who were monitored for reactogenicity with an electronic diary.

Table 10: Study 2 – Frequency of Solicited Local Reactions Within 7 Days After Each Dose of COMIRNATY – Adolescents 12 to 15 Years of Age – Safety Population*

Local Reaction	COMIRNATY Dose 1 N[a]=1,127 n[b] (%)	Placebo Dose 1 N[a]=1,127 n[b] (%)	COMIRNATY Dose 2 N[a]=1,097 n[b] (%)	Placebo Dose 2 N[a]=1,078 n[b] (%)
Redness				
Any (>2 cm)	65 (5.8)	12 (1.1)	55 (5.0)	10 (0.9)
Severe[c]	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Swelling				
Any (>2 cm)	78 (6.9)	11 (1.0)	54 (4.9)	6 (0.6)
Severe[c]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pain at the injection site				
Any	971 (86.2)	263 (23.3)	866 (78.9)	193 (17.9)
Severe[d]	11 (1.0)	0 (0.0)	7 (0.6)	0 (0.0)
Any local reaction[e]	976 (86.6)	271 (24.0)	872 (79.5)	198 (18.4)

Note: Reactions were collected in the electronic diary (e-diary) from Day 1 to Day 7 after vaccination.
a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.
b. n = Number of participants with the specified reaction.
c. Severe: >10.0 cm.
d. Severe: prevents daily activity.
e. Any local reaction: any redness >2.0 cm, any swelling >2.0 cm, or any pain at the injection site
* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.

Table 11: Study 2 – Frequency of Solicited Systemic Reactions Within 7 Days After Each Dose of COMIRNATY – Adolescents 12 to 15 Years of Age – Safety Population*				
Systemic Reaction	**COMIRNATY Dose 1 N[a]=1,127 n[b] (%)**	**Placebo Dose 1 N[a]=1,127 n[b] (%)**	**COMIRNATY Dose 2 N[a]=1,097 n[b] (%)**	**Placebo Dose 2 N[a]=1,078 n[b] (%)**
Fever				
≥38.0°C	114 (10.1)	12 (1.1)	215 (19.6)	7 (0.6)
>38.9°C	11 (1.0)	2 (0.2)	25 (2.3)	1 (0.1)
Fatigue				
Any	677 (60.1)	457 (40.6)	726 (66.2)	264 (24.5)
Severe[c]	15 (1.3)	8 (0.7)	26 (2.4)	4 (0.4)
Headache				
Any	623 (55.3)	396 (35.1)	708 (64.5)	263 (24.4)
Severe[c]	11 (1.0)	9 (0.8)	22 (2.0)	1 (0.1)
Chills				
Any	311 (27.6)	109 (9.7)	455 (41.5)	73 (6.8)
Severe[c]	5 (0.4)	2 (0.2)	20 (1.8)	0 (0.0)
Vomiting				
Any	31 (2.8)	10 (0.9)	29 (2.6)	12 (1.1)
Severe[d]	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhea				
Any	90 (8.0)	82 (7.3)	65 (5.9)	43 (4.0)
Severe[e]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
New or worsened muscle pain				
Any	272 (24.1)	148 (13.1)	355 (32.4)	90 (8.3)
Severe[c]	2 (0.2)	0 (0.0)	6 (0.5)	2 (0.2)
New or worsened joint pain				
Any	109 (9.7)	77 (6.8)	173 (15.8)	51 (4.7)
Severe[c]	1 (0.1)	0 (0.0)	4 (0.4)	0 (0.0)
Any systemic reactions[f]	877 (77.8)	636 (56.4)	904 (82.4)	439 (40.7)
Use of antipyretic or pain medication	413 (36.6)	111 (9.8)	557 (50.8)	95 (8.8)

Note: Events and use of antipyretic or pain medication were collected in the electronic diary (e-diary) from Day 1 to Day 7 after each dose.
a. N = Number of participants reporting at least 1 yes or no response for the specified event after the specified dose.
b. n = Number of participants with the specified reaction.
c. Severe: prevents daily activity.
d. Severe: requires intravenous hydration.
e. Severe: 6 or more loose stools in 24 hours.
f. Any systemic reaction: any fever ≥38.0°C, any fatigue, any vomiting, any chills, any diarrhea, any headache, any new or worsened muscle pain, or any new or worsened joint pain
* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.

Unsolicited Adverse Events

In the analysis of Study 2 of all unsolicited adverse events reported following any dose, through 1 month after Dose 2, in adolescents 12 to 15 years of age (N=2260; 1,131 COMIRNATY group vs. 1,129 placebo group), those assessed as adverse reactions not already captured by solicited local and systemic reactions were lymphadenopathy (9 (0.8%) vs. 2 (0.2%)), and nausea (5 (0.4%) vs. 1 (0.1%)).

In analyses of all unsolicited adverse events in Study 2 from Dose 1 up to the participant unblinding date, 69.0% of study participants 12 through 15 years of age had at least 4 months of follow-up after Dose 2. Among participants 12 through 15 years of age who received at least one dose of study vaccine, 1,131 of whom received COMIRNATY and 1,129 of whom received placebo, unsolicited adverse events were reported by 95 (8.4%) participants in the COMIRNATY group and 113 (10.0%) participants in the placebo group.

Non-serious adverse events from Dose 1 through up to 30 days after Dose 2 in ongoing follow-up were reported by 5.8% of COMIRNATY recipients and by 5.8% of placebo recipients. From Dose 1 through 30 days after Dose 2, reports of lymphadenopathy plausibly related to the study intervention were imbalanced, with notably more cases in the COMIRNATY group (7) vs. the placebo group (1). In the analysis of blinded, placebo-controlled follow-up, there were no other notable patterns or numerical imbalances between treatment groups for specific categories of non-serious adverse events (including other neurologic or neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to COMIRNATY. In the analysis of unblinded follow-up, there were no notable patterns of specific categories of non-serious adverse events that would suggest a causal relationship to COMIRNATY.

Serious Adverse Events

In Study 2, among participants 12 through 15 years of age who had received at least 1 dose of vaccine or placebo (COMIRNATY = 1,131; placebo = 1,129), serious adverse events from Dose 1 up to the participant unblinding date in ongoing follow-up were reported by 10 (0.9%) COMIRNATY recipients and 2 (0.2%) placebo recipients. In these analyses, 69.0% (786 COMIRNATY and 773 placebo) of study participants had at least 4 months of follow-up after Dose 2. In the analysis of blinded, placebo-controlled follow-up, there were no notable patterns between treatment groups for specific categories of serious adverse events (including neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to COMIRNATY. In the analysis of unblinded follow-up, there were no notable patterns of specific categories of serious adverse events that would suggest a causal relationship to COMIRNATY. In study 2, a 16-year-old male was diagnosed with myopericarditis 3 days after his 2nd dose. The participant was treated and recovered.

8.5 Post-Market Adverse Reactions

The following adverse reactions have been identified during post authorization use of COMIRNATY.

Cardiac Disorders: myocarditis and/or pericarditis (see **7 WARNING AND PRECAUTIONS**)

Immune System Disorders: severe allergic reactions, including anaphylaxis

Musculoskeletal and Connective Tissue Disorders: pain in extremity (arm)

Nervous System Disorders: Facial paralysis / Bell's Palsy, hypoesthesia, paresthesia

Skin and subcutaneous tissue disorders and other hypersensitivity reactions: skin rash, pruritus, urticaria, angioedema, erythema multiforme

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to product exposure. They are included because: a) they represent reactions that are known to occur following immunizations generally; b) they are potentially serious; or c) on the basis of their frequency of reporting.

9 DRUG INTERACTIONS

No interaction studies have been performed. There is no information on the co-administration of COMIRNATY Original & Omicron BA.4/BA.5 with other vaccines.

Do not mix COMIRNATY Original & Omicron BA.4/BA.5 with other vaccines/products in the same syringe.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

The nucleoside-modified messenger RNA in tozinameran encodes for the viral spike (S) protein of SARS-CoV-2 Original strain and famtozinameran (mRNA) encodes the viral spike of SARS-CoV-2 Omicron variant lineages BA.4 and BA.5 (Omicron BA.4/BA.5). The mRNAs are formulated in lipid nanoparticles, which enable delivery of the RNA into host cells to allow expression of the SARS-CoV-2 S antigen. The vaccine elicits both neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19 disease.

11 STORAGE, STABILITY AND DISPOSAL

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

Do not refreeze thawed vials.

For 12 Years and Older: DO NOT DILUTE (Vials with Gray Cap and Gray Label Border)

Vial Storage Prior to Use

Cartons of COMIRNATY Original & Omicron BA.4/BA.5 multiple dose vials (for 12 years and older: DO NOT DILUTE) may arrive frozen at ultra-cold conditions in thermal containers with dry ice.

Once received, frozen vials may be immediately transferred to the refrigerator [2°C to 8°C (35°F to 46°F)], thawed and stored for a single period of up to 10 weeks within the 12-month shelf-life. The 10-week refrigerated expiry date should be recorded on the carton at the time of transfer. A carton of 10 vials may take up to 6 hours to thaw at this temperature.

Alternatively, frozen vials may be stored in an ultra-low temperature freezer at -90°C to -60°C (-130°F to -76°F) for up to 12 months from the date of manufacture. Do not store vials at -25°C to -15°C (-13°F to 5°F). Once vials are thawed they should not be refrozen.

Cartons of COMIRNATY Original & Omicron BA.4/BA.5 multiple dose vials (for 12 years and older: DO NOT DILUTE) may also arrive at 2°C to 8°C (35°F to 46°F) . If received at 2°C to 8°C, they should be stored at 2°C to 8°C. Check that the carton has been updated to reflect the 10-week refrigerated expiry date.

Regardless of storage condition, vaccine should not be used after 12 months from the date of manufacture printed on the vial and cartons.

Vial Storage During Use

If not previously thawed at 2°C to 8°C (35°F to 46°F), allow vials to thaw at room temperature [up to 25°C (77°F)] for 30 minutes.

COMIRNATY Original & Omicron BA.4/BA.5 multiple dose vials (for 12 years and older: DO NOT DILUTE) may be stored at room temperature up to 25°C (77°F) for a total of 12 hours prior to the first puncture.

DO NOT DILUTE PRIOR TO USE.

After first puncture, the vial should be stored at 2°C to 25°C (35°F to 77°F). Vials should be discarded 12 hours after first puncture.

Thawed vials can be handled in room light conditions.

Transportation of Vials

If local redistribution is needed, full cartons containing unpunctured vials may be transported at -90°C to -60°C (-130°F to -76°F); full cartons or individual unpunctured vials may also be transported at 2°C to 8°C (35°F to 46°F).

12 SPECIAL HANDLING INSTRUCTIONS

COMIRNATY Original & Omicron BA.4/BA.5 multiple dose vials contain a frozen suspension that does not contain preservative and must be thawed prior to administration.

Careful attention should be paid to the vial cap colour and label border and the appropriate corresponding instructions must be followed. For important information on handling and preparation for administration, please refer to **11 STORAGE, STABILITY AND DISPOSAL** and **4 DOSAGE AND ADMINISTRATION**.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance:

Proper name: COVID-19 Vaccine, mRNA

International nonproprietary name: Tozinameran (original strain) and Famtozinameran (Omicron BA.5/BA.5 strain)

Product Characteristics:

COMIRNATY Original & Omicron BA.4/BA.5 (COVID-19 mRNA Vaccine, Bivalent (Original and Omicron BA.4/BA.5)) contains highly purified single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates encoding the viral spike (S) protein of the SARS-CoV-2 original strain and Omicron variant lineages BA.4 and BA.5 (Omicron BA.4/BA.5).

This vaccine is a white to off-white frozen suspension provided as a multiple dose vial which does not require dilution prior to use.

For 12 Years and Older: **DO NOT DILUTE** (Vials with Gray Cap and Gray Label Border)
One vial (2.25 mL) contains 6[†] doses of 0.3 mL. **Do not dilute prior to use**. One dose (0.3 mL) contains 30 micrograms of COVID-19 mRNA (15 mcg Original and 15 mcg Omicron BA.4/BA.5), embedded in lipid nanoparticles.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

The effectiveness of a booster dose of COMIRNATY Original & Omicron BA.4/BA.5 for individuals 12 years of age and older is inferred from studies of a booster dose of COMIRNATY Original/Omicron BA.1 in individuals >55 years of age and also data from studies of a booster dose of monovalent Omicron BA.1 in individuals 18 to ≤55 years of age.

14.1.1 COMIRNATY Original/Omicron BA.1 (15/15mcg)

Relative vaccine immunogenicity in participants greater than 55 years of age – after a second booster dose of COMIRNATY bivalent vaccine

The safety, reactogenicity, and immunogenicity of COMIRNATY Original/Omicron BA.1 booster dose are evaluated in an ongoing Phase 3 randomized observer-blinded Substudy in participants >55 years of age (Study 4). In this study, 305 participants received COMIRNATY Original/Omicron BA.1 30 mcg booster dose and 305 participants received the COMIRNATY 30 mcg booster dose. Overall, of the COMIRNATY Original/Omicron BA.1 group, 46.9% were female, 53.1% were male, 89.8% were White, and 14.8% were Hispanic or Latino. The median age was 67 years (range: 56 to 85 years).

[†] Low dead volume syringes and/or needles can be used to extract 6 doses from a single vial. If standard syringes and needles are used, there may not be sufficient volume to extract a 6th dose from a single vial.

Demographic and baseline characteristics were similar between COMIRNATY Original/Omicron BA.1 30 mcg and COMIRNATY 30 mcg groups.

In Study 4, COMIRNATY Original/Omicron BA.1 was administered as a second booster dose. The median time between a first booster dose and the second booster dose with COMIRNATY Original/Omicron BA.1 was 6.3 months (range: 4.7 to 11.5 months).

14.1.2 COMIRNATY (30 mcg)

The safety and efficacy of COMIRNATY were evaluated in Study 2, a multicenter, multinational, Phase 1/2/3, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate-selection and efficacy study in participants 12 years of age and older. Randomization 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 hospitalization for worsening disease during the 6 weeks before enrollment, were included as were participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV).

In the Phase 2/3 portion of Study 2, based on data accrued through November 14, 2020, approximately 44,000 participants 12 years of age and older were randomized equally and received 2 doses of COMIRNATY or placebo. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. The majority (93.1%) of vaccine recipients received the second dose 19 days to 23 days after Dose 1. Participants are planned to be followed for up to 24 months, for assessments of safety and efficacy against COVID-19.

The population for the analysis of the primary efficacy endpoint included 36,621 participants 12 years of age and older (18,242 in the COMIRNATY group and 18,379 in the placebo group) who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose. Table 12 presents the specific demographic characteristics in the studied population.

Table 12: Demographics (Population for the Primary Efficacy Endpoint)[a] (Data Accrued Through November 14, 2020)

	COMIRNATY (N=18,242) n (%)	**Placebo (N=18,379) n (%)**
Sex		
Male	9,318 (51.1)	9,225 (50.2)
Female	8,924 (48.9)	9,154 (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 to 15 years	46 (0.3)	42 (0.2)
16 to 64 years	14,216 (77.9)	14,299 (77.8)
65 to 74 years	3,176 (17.4)	3,226 (17.6)
≥75 years	804 (4.4)	812 (4.4)

Table 12: Demographics (Population for the Primary Efficacy Endpoint)[a] (Data Accrued Through November 14, 2020)		
	COMIRNATY (N=18,242) n (%)	**Placebo (N=18,379) n (%)**
Race		
White	15,110 (82.8)	15,301 (83.3)
Black or African American	1,617 (8.9)	1,617 (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[b]	534 (2.9)	516 (2.8)
Ethnicity		
Hispanic or Latino	4,886 (26.8)	4,857 (26.4)
Not Hispanic or Latino	13,253 (72.7)	13,412 (73.0)
Not reported	103 (0.6)	110 (0.6)
Comorbidities[c]		
Yes	8,432 (46.2)	8,450 (46.0)
No	9,810 (53.8)	9,929 (54.0)

a. All eligible randomized participants who receive all vaccination(s) as randomized 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. Includes multiracial and not reported.
c. 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)

To assess boostability, a subset of Study 2 participants were enrolled in selected sites, and 306 participants aged 18 to 55 years were re-randomized to receive a booster dose approximately 6 months after completion of the two-dose regimen (median interval between dose 2 and booster dose – 6.8 months; range 4.8 to 8.0 months). The median age at the time of booster vaccination was 42.0 years, and 46.3% of participants were male.

In 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 at least 6 months after the second dose. The median age at the time of booster vaccination was 53 years, and 49% of the participants were male.

14.2 Study Results

14.2.1 COMIRNATY Original/Omicron BA.1 (15/15mcg)

14.2.1.1 Relative Vaccine Immunogenicity in Participants Older Than 55 Years of Age – After a Second Booster Dose (4th dose) of COMIRNATY Original/Omicron BA.1

The safety, reactogenicity, and immunogenicity of COMIRNATY Original/Omicron BA.1 booster dose are evaluated in an ongoing Phase 3 randomized observer-blinded study in participants >55 years of age (Study 4). In Substudy E, the vaccine test group (bivalent vaccine) consisted of participants that were administered the COMIRNATY Original/Omicron BA.1 vaccine as a second booster dose (30 mcg, COMIRNATY Original/Omicron BA.1 [15 mcg and 15 mcg]) and the comparator group (COMIRNATY) were administered COMIRNATY (30 mcg) as a second booster dose.

Immunobridging analyses compared the neutralizing antibody titers 1 month following the second booster dose with COMIRNATY Original/ Omicron BA.1 (N = 177) to the corresponding titers 1 month following the second booster dose with COMIRNATY (N = 167) against the Omicron BA.1 subvariant.

In Substudy E, the primary analysis was based on the immunogenicity set (a random sample of 230 participants in each vaccine group selected from the expanded cohort), which included participants with no evidence of SARS-CoV-2 infection up to 1 month after Dose 4.

The Substudy E met its co-primary objectives of superiority and non-inferiority. Superiority of COMIRNATY Original/Omicron BA.1 to COMIRNATY was achieved as the lower bound of the 2-sided 95% CI for GMR was >1. The estimated 1 month neutralizing antibody GMTs against Omicron BA.1 were 711.0 (95%CI: 588.3, 859.2) and 455.8 (95%CI: 365.9, 567.6) in the COMIRNATY Original/Omicron BA.1 and COMIRNATY second booster groups, respectively, and the GMR was 1.56 (95%CI: 1.17, 2.08). Noninferiority with respect to seroresponse rate (SRR) of COMIRNATY Original/Omicron BA.1 to COMIRNATY was also met as the lower bound of the 2-sided 95% CI for the difference in seroresponse rates was greater than the prespecified noninferiority margin of -5%. The Omicron BA.1 SRRs were 71.6% (95%CI: 64.2, 78.3) and 57.0% (95%CI: 48.7, 65.1), 1 month post vaccination in the COMIRNATY Original/Omicron BA.1, and COMIRNATY, respectively, and the SRR difference was 14.6% (95%CI: 4.0, 24.9). The findings are summarized in Table 13 and Table 14.

Table 13: Substudy E - Geometric mean ratios for between vaccine group comparison – participants without evidence of infection up to 1 month after Dose 4 – expanded cohort – immunogenicity subset – participants older than 55 years of age – evaluable immunogenicity population

Assay	Vaccine group (as randomized)	Sampling time point[a]	N[b]	GMT (95% CI[c])	GMR (95% CI[d])
SARS-CoV-2 neutralization assay - Omicron BA.1 - NT50 (titre)	COMIRNATY (30 mcg)	1 month	163	455.8 (365.9, 567.6)	
	COMIRNATY bivalent (COMIRNATY Original 15 mcg + COMIRNATY Omicron BA.1 15 mcg)	1 month	178	711.0 (588.3, 859.2)	1.56 (1.17, 2.08)

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titre; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Immunogenicity subset = a random sample of 230 participants in each vaccine group selected from the expanded cohort.
Note: Participants who had no serological or virological evidence (prior to the 1 month post–study vaccination blood sample collection) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] result negative at the study vaccination and the 1 month post–study vaccination visits, negative NAAT [nasal swab] result at the study vaccination visit, and any unscheduled visit prior to the 1 month post–study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.

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

Table 14: Substudy E - Number (%) of participants achieving seroresponse – participants without evidence of infection up to 1 month after Dose 4 – expanded cohort – immunogenicity subset – participants greater than 55 years of age – evaluable immunogenicity population

Assay	Vaccine group (as randomized)	Sampling time point[a]	N[b]	n[c] (%) (95% CI[d])	Difference %[e] (95% CI[f])
SARS-CoV-2 neutralization assay - Omicron BA.1 - NT50 (titre)	COMIRNATY (30 mcg)	1 month	149	85 (57.0) (48.7, 65.1)	
	COMIRNATY bivalent (Original 15 mcg + Omicron BA.1 15 mcg)	1 month	169	121 (71.6) (64.2, 78.3)	14.6 (4.0, 24.9)

Abbreviations: LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titre; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Immunogenicity subset = a random sample of 230 participants in each vaccine group selected from the expanded cohort.
Note: Seroresponse is defined as achieving ≥ 4-fold rise from baseline (before the study vaccination). If the baseline measurement is below the LLOQ, the postvaccination measure of ≥ 4 × LLOQ is considered a seroresponse.
Note: Participants who had no serological or virological evidence (prior to the 1 month post–study vaccination blood sample collection) of past SARS-CoV-2 infection (i.e. N-binding antibody [serum] result negative at the study vaccination and the 1 month post–study vaccination visits, negative NAAT [nasal swab] result at the study vaccination visit, and any unscheduled visit prior to the 1 month post–study vaccination blood sample collection) and had no medical history of COVID-19 were included in the analysis.

a. Protocol-specified timing for blood sample collection.
b. N = number of participants with valid and determinate assay results for the specified assay at both the pre-vaccination time point and the given sampling time point. This value is the denominator for the percentage calculation.

c. n = Number of participants with seroresponse at 1 month after vaccination for the given assay.
d. Exact 2-sided CI based on the Clopper and Pearson method.
e. Difference in proportions, expressed as a percentage (vaccine group in the corresponding row - Comirnaty [30 mcg]).
f. 2-sided CI based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.

14.2.2 COMIRNATY (30 mcg)

14.2.2.1 Efficacy and Immunogenicity in Participants 16 Years of Age and Older

14.2.2.1.1 Efficacy in Participants 16 Years of Age and Older – After Two Doses

Primary Vaccine Efficacy Analysis (Based on Cut-off Date of November 14, 2020)

At the time of the primary efficacy analysis, participants had been followed for symptomatic COVID-19 for at least 2,214 person-years in the COMIRNATY group and at least 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 primary endpoint was defined as any symptomatic COVID-19 case[1] confirmed by Reverse Transcription-Polymerase Chain Reaction (RT-PCR). The population for the analysis of the primary efficacy endpoint included participants who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose (first primary efficacy endpoint), as well as participants with and without evidence of prior infections with SARS-CoV-2 through 7 days after the second dose (second primary efficacy endpoint). The pre-specified success criterion for vaccine efficacy was met. The vaccine efficacy information is presented in Table 15.

Table 15: Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Age Subgroup – Participants Without Evidence of Infection and Participants With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population (Data Accrued Through November 14, 2020)

First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection*			
Subgroup	**COMIRNATY N[a]=18,198 Cases (n1[b]) Surveillance Time[c] (n2[d])**	**Placebo N[a]=18,325 Cases (n1[b]) Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI)**
All participants[e]	8 2.214 (17,411)	162 2.222 (17,511)	95.0 (90.3, 97.6)[f]
16 through 64 years	7 1.706 (13,549)	143 1.710 (13,618)	95.1 (89.6, 98.1)[g]
65 years and older	1 0.508 (3,848)	19 0.511 (3,880)	94.7 (66.7, 99.9)[g]

[1] Case definition defined by Study 2 protocol: (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, diarrhea or vomiting.

Table 15: 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 (Data Accrued Through November 14, 2020)

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

Subgroup	COMIRNATY N[a]=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)
All participants[e]	9 2.332 (18,559)	169 2.345 (18,708)	94.6 (89.9, 97.3)[f]
16 through 64 years	8 1.802 (14,501)	150 1.814 (14,627)	94.6 (89.1, 97.7)[g]
65 years and older	1 0.530 (4,044)	19 0.532 (4,067)	94.7 (66.8, 99.9)[g]

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting).
Abbreviations: NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
* Participants who had no evidence of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
a. N = number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. No confirmed cases were identified in adolescents 12 to 15 years of age.
f. Two-sided credible interval for vaccine efficacy (VE) was calculated using a beta-binomial model with a beta (0.700102, 1) prior for $\theta=r(1-VE)/(1+r(1-VE))$, where r is the ratio of surveillance time in the active vaccine group over that in the placebo group.
g. Two-sided confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted to the surveillance time.

Updated Vaccine Efficacy (Based on Cut-off Date of March 13, 2021)

Updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up through March 13, 2021, representing up to 6 months of follow-up after Dose 2 for participants in the efficacy population. There were 77 confirmed COVID-19 cases identified in the COMIRNATY and 850 in the placebo groups, respectively. In this analysis, compared to placebo, the vaccine efficacy of COMIRNATY in participants without evidence of SARS-CoV-2 infection prior to 7 days after Dose 2 was 91.3% (95% confidence interval of 89.0% to 93.2%); in participants 65 years of age and older without evidence of prior infection vaccine efficacy was 94.5% (two-sided 95% confidence interval 88.3% to 97.8%). The vaccine efficacy of COMIRNATY in participants with or without evidence of prior infection was 91.1% (95% confidence interval: 88.8% to 93.0%) with 81 COVID-19 cases in the COMIRNATY group compared to 873 cases in the placebo group.

Efficacy Against Severe COVID-19 (Based on Cut-off Date of March 13, 2021)

Secondary efficacy analyses in Study 2 supported benefit of COMIRNATY in preventing severe COVID-19. During blinded placebo-controlled follow-up through March 13, 2021, the vaccine efficacy against severe COVID 19 (as defined by the study protocol) in participants **with or without evidence** of SARS-CoV-2 infection prior to 7 days after Dose 2 was 95.3% (95% CI: 70.9%, 99.9%) with 1 and 21 cases in the vaccine and placebo groups, respectively. The COVID-19 case counts in participants without prior SARS-CoV-2 infection were the same as those in participants with or without prior SARS-CoV-2 infection in both the COMIRNATY and placebo groups.

14.2.2.1.2 Efficacy and Immunogenicity in Participants 16 Years of Age and Older – After Booster Dose

Immunogenicity in Participants 18 to 55 Years of Age – After Booster Dose

Noninferiority of immune responses 1 month after a COMIRNATY booster dose compared to 1 month after completion of the primary 2-dose series was assessed, in a subset of participants enrolled at selected sites in the US, by evaluating SARS-CoV-2 50% neutralizing titers (NT50) against the reference strain. Immunogenicity was evaluated in subjects who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the booster vaccination. The analysis demonstrated noninferior immune responses 1 month after a booster dose compared to 1 month after Dose 2 in individuals 18 through 55 years of age (Table 16).

Table 16: SARS-CoV-2 neutralization assay - NT50 (titer)† – GMT and seroresponse rate comparison of 1 month after booster dose to 1 month after primary series – participants without evidence of infection up to 1 month after booster dose* – booster dose evaluable immunogenicity population

		COMIRNATY Sampling Time Point		1 month after booster dose/ - 1 month after primary series	Met noninferiority objective
Assay	n	1 month after booster dose (95% CI)	1 month after Dose 2 (95% CI)	(97.5% CI)	(Y/N)
Geometric mean 50% neutralizing titer (GMT[b])	210[a]	2,476.4[b] (2,210.1, 2774.9)	753.7[b] (658.2, 863.1)	3.29[c] (2.76, 3.91)	Y[d]
Seroresponse rate (%) for 50% neutralizing titer	198[e]	197[f] 99.5% (97.2%, 100.0%)	194[f] 98.0% (94.4%, 99.4%)	1.5%[g] (-0.7%, 3.7%[h])	Y[i]

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; Y/N = yes/no.

† SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

* Participants who had no serological or virological evidence (up to 1 month after receipt of a booster dose of COMIRNATY) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative and SARS-CoV-2 not detected by NAAT [nasal swab]) and had a negative NAAT (nasal swab) at any unscheduled visit up to 1 month after the booster dose were included in the analysis.
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 titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
c. GMRs and 2-sided 97.5% CIs were calculated by exponentiating the mean differences in the logarithms of the assay and the corresponding CIs (based on the Student t distribution).
d. Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the GMR is >0.67 and the point estimate of the GMR is ≥0.80.
e. n = Number of participants with valid and determinate assay results for the specified assay at baseline, 1 month after Dose 2 and 1 month after the booster dose within specified window. These values are the denominators for the percentage calculations.
f. Number of participants with seroresponse for the given assay at the given dose/sampling time point. Exact 2-sided CI based on the Clopper and Pearson method. Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result ≥4 × LLOQ is considered a seroresponse.
g. Difference in proportions, expressed as a percentage (1 month after booster dose – 1 month after Dose 2).
h. Adjusted Wald 2-sided CI for the difference in proportions, expressed as a percentage.
i. Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the percentage difference is >-10%.

Relative Vaccine Efficacy in Participants 16 Years of Age and Older – After Booster Dose

An interim efficacy analysis of Study 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 and evaluated confirmed COVID-19 cases accrued from at least 7 days after booster vaccination up to a data cut-off date of 5 October 2021, which represents a median of 2.5 months post-booster follow-up. Vaccine efficacy of the COMIRNATY booster dose after the primary series relative to the placebo booster group who only received the primary series dose was assessed. The relative vaccine efficacy information for participants 16 years of age and older is presented in Table 17.

Table 17: Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Booster Vaccination – Participants 16 Years of Age and Older Without Evidence of Infection and Participants With or Without Evidence of Infection Prior to 7 Days After Booster Vaccination – Evaluable Efficacy Population

First COVID-19 occurrence from 7 days after booster dose in participants without evidence of prior SARS-CoV-2 infection*			
	COMIRNATY N[a]=4,695 Cases (n1[b]) Surveillance Time[c] (n2[d])	**Placebo N[a]=4,671 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	6 0.823 (4,659)	123 0.792 (4,614)	95.3 (89.5, 98.3)
First COVID-19 occurrence from 7 days after booster dose in participants with or without evidence of prior SARS-CoV-2 infection			
	COMIRNATY N[a]=4,993 Cases (n1[b]) Surveillance Time[c] (n2[d])	**Placebo N[a]=4,952 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	7 0.871 (4,934)	124 0.835 (4,863)	94.6 (88.5, 97.9)

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; diarrhea; vomiting).
* Participants who had no serological or virological evidence (prior to 7 days after receipt of the booster vaccination) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visit 1, and had a negative NAAT [nasal swab] at any unscheduled visit prior to 7 days after booster vaccination) were included in the analysis.
a. N = Number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after the booster vaccination to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Relative vaccine efficacy of the COMIRNATY booster group relative to the placebo group (non-booster).
f. Two-sided confidence interval (CI) for relative vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.

14.2.2.2 Efficacy and Immunogenicity in Adolescents 12 to 15 Years of Age

14.2.2.2.1 Efficacy and Immunogenicity in Adolescents 12 to 15 Years of Age – After Two Doses

Efficacy

The vaccine efficacy in participants 12 to 15 years of age was evaluated on a subgroup analysis of Study 2 based on a cut-off date of March 13, 2021 (Table 18).

Table 18: 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 (Data Accrued Through March 13, 2021), Adolescents 12 to 15 Years of Age Evaluable Efficacy (7 Days) Population

First COVID-19 occurrence from 7 days after Dose 2 in adolescents 12 to 15 years of age without evidence of prior SARS-CoV-2 infection*			
	COMIRNATY N[a]=1,005 Cases (n1[b]) Surveillance Time[c] (n2[d])	**Placebo N[a]=978 Cases (n1[b]) Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI[e])**
Adolescents 12 to 15 Years of Age	0 0.154 (1,001)	16 0.147 (972)	100.0 (75.3, 100.0)
First COVID-19 occurrence from 7 days after Dose 2 in adolescents 12 to 15 years of age with or without* evidence of prior SARS-CoV-2 infection			
	COMIRNATY N[a]=1,119 Cases (n1[b]) Surveillance Time[c] (n2[d])	**Placebo N[a]=1,110 Cases (n1[b]) Surveillance Time[c] (n2[d])**	**Vaccine Efficacy % (95% CI[e])**
Adolescents 12 to 15 Years of Age	0 0.170 (1,109)	18 0.163 (1094)	100.0 (78.1, 100.0)

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

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

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

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

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

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

e. Confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.

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.

In the adolescent group, in efficacy analyses in the evaluable efficacy population based on cases reported from at least 7 days after Dose 2 through the data cut-off date (02 September 2021), representing a median of 4.4 (range 0-10.8) months of follow-up after Dose 2, there were 0 confirmed COVID-19 cases identified in the COMIRNATY and 28 in the placebo groups, respectively. In this analysis, compared to placebo, the estimated VE against confirmed COVID-19 was 100% (95% CI: 86.8%, 100%) for individuals without evidence of prior SARS-CoV-2 infection before and during vaccination regimen. The estimated VE against confirmed COVID-19 was 100% (2-sided 95% CI: 87.5%, 100%) for those with or without evidence of prior SARS-CoV-2 infection before and during vaccination regimen, with 0 COVID-19 cases in the COMIRNATY group compared to 30 cases in the placebo group.

Among participants without and with or without evidence of SARS-CoV-2 infection before and during the vaccination regimen (evaluable efficacy population), VE against COVID-19 occurring at least 7 days after Dose 2 was evaluated for demographic and risk subgroups, and the estimated VE was 100.0% for all subgroups.

Immunogenicity – After Two Doses

In Study 2, an analysis of SARS-CoV-2 50% neutralizing titers (NT50) 1 month after Dose 2 in a randomly selected subset of participants demonstrated non-inferior immune responses (within 1.5-fold) comparing adolescents 12 through 15 years of age to participants 16 through 25 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2 (Table 19).

Table 19: Summary of Geometric Mean Ratio for 50% Neutralizing Titer – Comparison of Adolescents 12 Through 15 Years of Age to Participants 16 Through 25 Years of Age (Immunogenicity Subset) –Participants Without Evidence of Infection up to 1 Month After Dose 2 – Dose 2 Evaluable Immunogenicity Population

		COMIRNATY		12 Through 15 Years/ 16 Through 25 Years	
		12 Through 15 Years n[a]=190	16 Through 25 Years n[a]=170		
Assay	**Time Point[b]**	**GMT[c] (95% CI[c])**	**GMT[c] (95% CI[c])**	**GMR[d] (95% CI[d])**	**Met Noninferiority Objective[e] (Y/N)**
SARS-CoV-2 neutralization assay - NT50 (titer)f	**1 month after Dose 2**	1,239.5 (1,095.5, 1,402.5)	705.1 (621.4, 800.2)	1.76 (1.47, 2.10)	Y

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic-acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Participants who had no serological or virological evidence (up to 1 month 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 NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit up to 1 month after Dose 2 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 titers 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 titers (Group 1 [12 through 15 years of age] – Group 2 [16 through 25 years of age]) and the corresponding CI (based on the Student t distribution).
e. Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67.
f. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

15 MICROBIOLOGY

No microbiological information is required for this product.

16 NON-CLINICAL TOXICOLOGY

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

General Toxicology:

In a repeat-dose toxicity study, rats were administered three once weekly doses of 30 mcg/animal (0.06 mL of a vaccine formulation containing the same quantity of nucleoside-modified messenger ribonucleic acid (mRNA) and other ingredients included in a single human dose) of COMIRNATY by intramuscular injection. Vaccine administration resulted in transient erythema and edema at the site of injection, as well as increased cellularity in draining and inguinal lymph nodes, spleen, and bone marrow, along with transiently increased body temperature, increased white blood counts, and decreased reticulocyte counts coupled with decreased red blood cell mass. Clinical chemistry changes (e.g., increased acute phase protein levels) indicated an acute phase response. These changes are consistent with an expected immunostimulatory response following intramuscular administration of a vaccine. Transient periportal hepatocyte vacuolation was also observed without evidence of liver injury. Full or partial recovery from all findings was observed following a 3-week recovery period.

Carcinogenicity:

Carcinogenic potential was not assessed, as carcinogenicity studies were not considered relevant to this vaccine.

Genotoxicity:

Genotoxic potential was not assessed, as genotoxicity studies were not considered relevant to this vaccine.

Reproductive and Developmental Toxicology:

In a reproductive and developmental toxicity study, 30 mcg/animal (0.06 mL of a vaccine formulation containing the same quantity of nucleoside-modified messenger ribonucleic acid (mRNA) and other ingredients included in a single human dose) of COMIRNATY was administered to female rats by the intramuscular route on four occasions: 21 and 14 days prior to mating, and on gestation days 9 and 20. No vaccine-related adverse effects on female fertility, fetal development, or postnatal development were reported in the study.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

COMIRNATY® Original & Omicron (BA.4/BA.5)

COVID-19 mRNA Vaccine, Bivalent (Original and Omicron BA.4/BA.5), Suspension for Intramuscular Injection

This leaflet is a summary and will not tell you everything about this vaccine. Talk to your/your child's healthcare professional about your/your child's medical condition and treatment and ask if there is any new information about **COMIRNATY Original & Omicron BA.4/BA.5**.

What is COMIRNATY Original & Omicron BA.4/BA.5 used for?

COMIRNATY Original & Omicron BA.4/BA.5 is a vaccine used to provide protection against COVID-19 disease caused by the SARS-CoV-2 virus.

COMIRNATY Original & Omicron BA.4/BA.5 can be given to people 12 years of age and older as a booster dose.

The safety and effectiveness of a booster dose of COMIRNATY Original & Omicron BA.4/BA.5 for individuals 12 years of age and older is inferred from studies of a booster dose of COMIRNATY Original/Omicron BA.1 in individuals >55 years of age and also data from studies of a booster dose of monovalent Omicron BA.1 in individuals 18 to ≤55 years of age.

How does COMIRNATY Original & Omicron BA.4/BA.5 work?

The vaccine causes our body to produce protection (such as antibodies) that prevent the COVID-19 virus from entering our cells to make us sick. The vaccine uses a new method (messenger RNA - mRNA, the genetic code for a piece of the virus) to help our bodies make protection against the virus. The vaccine is given by injection with a needle in the upper arm.

You cannot get COVID-19 from the vaccine.

As with any vaccine, COMIRNATY Original & Omicron BA.4/BA.5 may not fully protect all those who receive it. Even after you/your child have had the vaccine, continue to follow the recommendations of local public health officials to prevent spread of COVID-19.

What are the ingredients in COMIRNATY Original & Omicron BA.4/BA.5?

Medicinal ingredient: mRNA (tozinameran and famtozinameran)

Non-medicinal ingredients:

- ALC-0315 = ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate)
- ALC-0159 = 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide
- 1,2-distearoyl-sn-glycero-3-phosphocholine
- cholesterol
- sodium chloride
- sucrose
- tromethamine

- tromethamine hydrochloride
- water for injection

COMIRNATY Original & Omicron BA.4/BA.5 comes in the following dosage forms:

For 12 Years of Age and Older:

Vial with Gray Cap and Gray Label Border (DO NOT DILUTE): White to off-white suspension provided in a multiple dose vial of 6 doses of 0.3 mL, with 30 micrograms mRNA (15 mcg Original and 15 mcg Omicron BA.4/BA.5) each.

You/your child should not receive COMIRNATY Original & Omicron BA.4/BA.5 if:

- you/your child are allergic to any of the ingredients in this vaccine (see **What are the ingredients in COMIRNATY Original & Omicron BA.4/BA.5?**)
- you/your child had a severe allergic reaction after a previous dose of this vaccine
- you/your child have any symptoms that could be due to COVID-19. Talk with your/your child's healthcare professional about your/your child's symptoms and getting a COVID-19 test. Your/your child's healthcare professional will advise you when you/your child are able to receive the vaccine.

To help avoid side effects and ensure proper use, talk to your/your child's healthcare professional before you/your child receive COMIRNATY Original & Omicron BA.4/BA.5. Talk about any health conditions or problems you/your child may have, including if you/your child:

- have had any problems following a previous dose of COMIRNATY, COMIRNATY Original/Omicron BA.1 or COMIRNATY Original & Omicron BA.4/BA.5 such as an allergic reaction or breathing problems
- have any allergies
- have a weakened immune system due to a medical condition or are on a medicine that affects the immune system
- have previously had episodes of myocarditis and/or pericarditis
- are feeling nervous about the vaccination process or have ever fainted in association with an injection
- have a bleeding problem, bruise easily or use a blood thinning medication
- are pregnant, think you may be pregnant or plan to become pregnant
- are breast-feeding

Other warnings you should know about:

As with any vaccine, COMIRNATY Original & Omicron BA.4/BA.5 may not fully protect all those who receive it.

Some of the effects of vaccination mentioned under "***What are possible side effects from using COMIRNATY Original* & *Omicron BA.4/BA.5?"*** may temporarily affect your ability to drive or use machines. Wait until these effects have worn off before you drive or use machines.

Tell your/your child's healthcare professional about all the medicines you/your child take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

There is no information on the use of COMIRNATY Original & Omicron BA.4/BA.5 with other vaccines.

Tell your healthcare professional if you/your child have recently received any other vaccine.

How COMIRNATY Original & Omicron BA.4/BA.5 is given:

The vaccine is given as an injection of 0.3 mL, preferably into a muscle of the upper arm.

Usual dose:

For 12 Years of Age and Older

A booster dose of COMIRNATY Original & Omicron BA.4/BA.5 may be administered intramuscularly at least 3 to 6 months after completing the primary course of COMIRNATY and/or a previous booster dose of COMIRNATY in individuals 12 years of age or older.

If you have any further questions on the use of COMIRNATY Original & Omicron BA.4/BA.5, ask your healthcare professional.

Overdose:

In the event of suspected overdose with COMIRNATY Original & Omicron BA.4/BA.5, contact your regional poison control centre.

Missed Dose:

If you forget to go back to your healthcare professional at the scheduled time for your/your child's next dose, ask your/your child's healthcare professional for advice.

What are possible side effects from using COMIRNATY Original & Omicron BA.4/BA.5?

Like all vaccines, COMIRNATY Original & Omicron BA.4/BA.5 can cause side effects, although not everybody gets them.

Side effects may occur at the following frequencies:

Very common: may affect more than 1 in 10 people

- injection site pain, swelling
- tiredness
- headache
- muscle pain
- chills
- joint pain
- fever
- diarrhea

Common: may affect more than 1 in 100 and up to 1 in 10 people

- injection site redness
- nausea
- vomiting

Uncommon: may affect more than 1 in 1000 and up to 1 in 100 people

- enlarged lymph nodes
- feeling unwell
- arm pain
- feeling weak or lack of energy/sleepy
- decreased appetite
- excessive sweating
- night sweats

Non-severe allergic reactions (such as rash, itching, hives or swelling of the face), severe allergic reactions, facial paralysis / Bell's palsy, erythema multiforme (skin reaction or lesion; red spots or patches), hypoesthesia (reduced or loss of sensation) and paresthesia ("tingling sensation") have been reported.

These are not all the possible side effects you/your child may have when taking COMIRNATY Original & Omicron BA.4/BA.5. If you/your child experience any side effects not listed here, tell your/your child's healthcare professional.

There is a remote chance that COMIRNATY Original & Omicron BA.4/BA.5 could cause a severe allergic reaction. A severe allergic reaction would usually occur within a few minutes to one hour after getting a dose of COMIRNATY Original & Omicron BA.4/BA.5. For this reason, the vaccination provider may ask you/your child to stay at the place where the vaccine was received for monitoring after vaccination. Should you/your child develop any serious symptoms or symptoms that could be an allergic reaction, seek medical attention right away. Symptoms of an allergic reaction include:

- hives (bumps on the skin that are often very itchy)
- swelling of the face, tongue or throat
- difficulty breathing
- a fast heartbeat
- dizziness and weakness

If you/your child experience a severe allergic reaction, call 9-1-1, or go to the nearest hospital.

Your/your child's health care provider should inform your local public health department of any serious side effects after vaccination.

Reporting Suspected Side Effects for Vaccines

For the general public: Should you experience a side effect following immunization, please report it to your healthcare professional.

Should you require information related to the management of the side effect, please contact your healthcare professional. The Public Health Agency of Canada, Health Canada and Pfizer Canada ULC cannot provide medical advice.

For healthcare professionals: If a patient experiences a side effect following immunization, please complete the Adverse Events Following Immunization (AEFI) Form appropriate for your province/territory (https://www.canada.ca/en/public-health/services/immunization/reporting-adverse-events-following-immunization/form.html) and send it to your local Health Unit.

Storage:

COMIRNATY Original & Omicron BA.4/BA.5 should be stored, supplied and administered by a healthcare professional.

Keep out of reach and sight of children.

If you want more information about COMIRNATY Original & Omicron BA.4/BA.5**:**

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website [www.pfizer.ca], or by calling 1-800-463-6001 (Pfizer Medical Information).

This leaflet was prepared by Pfizer Canada ULC.

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