PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

NUVAXOVID ™ XBB.1.5

COVID-19 Vaccine (Recombinant protein, Adjuvanted)

Suspension for intramuscular injection

Multidose Vial, 5 mcg / 0.5 mL (per dose)

(contains 5 doses of 0.5 mL)

Active Immunizing Agent

ATC Classification: J07BN04

NUVAXOVID ™ XBB.1.5 COVID-19 Vaccine (Recombinant protein, Adjuvanted) vaccine is 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.

NUVAXOVID ™ XBB.1.5 COVID-19 Vaccine (Recombinant protein, Adjuvanted) vaccine 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 NUVAXOVID ™ XBB.1.5 COVID-19 Vaccine (Recombinant protein, Adjuvanted) vaccine please refer to Health Canada's COVID-19 vaccines and transfer portal. COVID-19 vaccines and treatments portal (canada.ca)

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Date of Initial Authorization:

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Submission Control Number: 278519

RECENT MAJOR LABEL CHANGES

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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

NUVAXOVID ™ XBB.1.5 (COVID-19 Vaccine (Recombinant protein, Adjuvanted)) is indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older.

The safety and effectiveness of NUVAXOVID XBB.1.5 for individuals 12 years of age and older is inferred from studies which evaluated the primary series and booster vaccination with NUVAXOVID and supported by a study of a booster dose of an investigational vaccine targeting the Omicron BA.5 variant of SARS-CoV-2 in individuals 18 years of age and older, and by a study of a booster dose of an investigational vaccine targeting the Omicron BA.1 variant of SARS-CoV-2 in individuals 18 to 64 years of age.

The National Advisory Committee on Immunization (NACI) provides additional guidance on the use of the COVID-19 vaccines in Canada. Please refer to the COVID-19 vaccine: Canadian Immunization Guide and current vaccine statements.

1.1 Pediatrics

The safety and efficacy of NUVAXOVID XBB.1.5 in individuals under 12 years of age have not yet been established. Clinical studies of NUVAXOVID included participants ≥12 years of age to <18 years of age and their data contributes to the overall assessment of safety and effectiveness of NUVAXOVID XBB.1.5 in this pediatric population. The safety and efficacy of NUVAXOVID XBB.1.5 in pediatric individuals ≥12 years of age to <18 years of age have not yet been established in clinical trials.

1.2 Geriatrics

Clinical studies of NUVAXOVID include participants 65 years of age and older and their data contribute to the overall assessment of the safety and effectiveness of NUVAXOVID XBB.1.5 (See 8 ADVERSE REACTIONS and 14 CLINICAL TRIALS). The safety and effectiveness of NUVAXOVID XBB.1.5 in geriatric individuals have not yet been established in clinical trials.

2 CONTRAINDICATIONS

NUVAXOVID XBB.1.5 is contraindicated in individuals who are hypersensitive to the active ingredient or to any ingredients in the formulation, including any non-medicinal ingredient, or component of the container. (For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING).

3 SERIOUS WARNINGS AND PRECAUTIONS

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

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

NUVAXOVID XBB.1.5 is a suspension for intramuscular injection that should be administered by a trained healthcare professional.

4.2 Recommended Dose and Dosage Adjustment

INDIVIDUALS WHO HAVE PREVIOUSLY BEEN VACCINATED WITH A COVID-19 VACCINE SERIES

NUVAXOVID XBB.1.5 is administered intramuscularly as a single dose (0.5 mL) for individuals 12 years of age and older who have been vaccinated with a previously or currently marketed Canadian COVID-19 vaccine primary series at least 6 months after the most recent dose of an authorized COVID-19 vaccine. No dose adjustment is required based on age.

INDIVIDUALS WHO HAVE NOT PREVIOUSLY BEEN VACCINATED WITH A COVID-19 VACCINE SERIES

NUVAXOVID XBB.1.5 is administered intramuscularly as a two-dose series of 0.5 mL each for individuals 12 years of age and older who have not been vaccinated with a previously or currently marketed Canadian COVID-19 vaccine primary series. The second dose is to be administered 3 weeks after the first dose.

There are no data available on the interchangeability of NUVAXOVID XBB.1.5 with other COVID-19 vaccines to complete the 2-dose vaccination series.

4.3 Reconstitution

NUVAXOVID XBB.1.5 must not be reconstituted, mixed with other medicinal products, or diluted.

4.4 Administration

Use aseptic techniques for preparation and administration to ensure the sterility of each dose.

NUVAXOVID XBB.1.5 is colourless to slightly yellow, clear to mildly opalescent suspension, free of particles.

- Gently swirl the multidose vial before and in between each dose withdrawal. Do not shake.
- Prior to administration, visually inspect the contents of the vial for visible particulate matter and/or discolouration prior to administration. Also, visually inspect the vial for cracks or any abnormalities, such as evidence of tampering. If any of these conditions exists, the vaccine should not be administered.

Each 0.5 mL dose is withdrawn into a sterile needle and sterile syringe to be administered by intramuscular injection, preferably in the deltoid muscle of the upper arm.

- Do not inject the vaccine intravascularly, subcutaneously, or intradermally.
- Do not mix the vaccine in the same syringe with any other vaccines or medicinal products.

- Do not pool excess vaccine from multiple vials.

NUVAXOVID XBB.1.5 does not contain a preservative. Store the opened vial between 2°C to 8°C for up to 12 hours or at room temperature (up to 25°C) for up to 6 hours after first needle puncture.

- Record the date and time of discard on the vial label.
- Discard this vaccine if not used within 12 hours after first puncture of the vial.

5 OVERDOSAGE

In the case of a suspected vaccine overdose, monitoring of vital functions and symptomatic treatment are recommended.

For management of a suspected drug overdose, 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.

Table 1: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intramuscular injection	Suspension One dose (0.5 mL) contains 5 mcg of SARS-CoV-2 recombinant spike protein (Omicron, XBB.1.5 strain) Multidose vial (2.5 mL, containing 5 doses of 0.5 mL)	• Disodium hydrogen phosphate heptahydrate • Hydrochloric acid (for adjustment of pH) • Polysorbate 80 • Sodium chloride • Sodium dihydrogen phosphate monohydrate • Sodium hydroxide (for adjustment of pH) • Water for Injection *For adjuvant:* • Cholesterol • Disodium hydrogen phosphate dihydrate • Phosphatidylcholine • Potassium chloride • Potassium dihydrogen phosphate • Sodium chloride

Composition

SARS-CoV-2 recombinant spike protein (Omicron, XBB.1.5 strain)	5 mcg
Matrix-M adjuvant (*Quillaja saponaria* saponins fraction-A and fraction-C)	50 mcg

NUVAXOVID XBB.1.5 does not contain any preservatives or human-derived materials.

NUVAXOVID XBB.1.5 is supplied as 2.5 mL of suspension in a clear glass vial (type I glass) with a stopper (bromobutyl rubber) and an aluminium overseal with blue plastic flip-off cap. The vials are packaged in a secondary carton containing a total of two (2) multidose vials per carton. Each 2.5 mL vial contains 5 doses of 0.5 mL.

7 WARNINGS AND PRECAUTIONS

General

Vaccination should be postponed in individuals suffering from an acute severe febrile illness or acute infection.

As with any vaccine, vaccination with NUVAXOVID XBB.1.5 may not protect all recipients.

Individuals may not be optimally protected until 7 days after their second dose. (See 14 CLINICAL TRIALS).

Acute Allergic Reactions

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

Close observation for at least 15 minutes is recommended following vaccination; 30 minutes is a preferred interval when there is a specific concern about a possible vaccine reaction. An additional dose of the vaccine should not be given to those who have experienced anaphylaxis to a prior dose of NUVAXOVID.

Cardiovascular

Myocarditis and Pericarditis

Myocarditis and pericarditis have been reported following NUVAXOVID administration.

Available data suggest that the course of myocarditis and pericarditis following NUVAXOVID administration is not different from myocarditis and pericarditis in general.

Available data cannot determine a causal association with NUVAXOVID XBB.1.5.

Vaccinated individuals (including parents or caregivers) should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination.

Hematologic

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

Driving and Operating Machinery

NUVAXOVID XBB.1.5 has no known influence on the ability to drive and use machines. However, some of the adverse reactions mentioned under 8 ADVERSE REACTIONS may temporarily affect the ability to drive or use machines.

Fertility

It is unknown whether NUVAXOVID XBB.1.5 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).

Immune

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

Syncope

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. Procedures should be in place to prevent injury from fainting and manage syncopal reactions.

7.1 Special Populations

7.1.1 Pregnant Women

The safety and efficacy of NUVAXOVID XBB.1.5 in pregnant women have not yet been established.

Administration of NUVAXOVID XBB.1.5 in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and fetus.

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to NUVAXOVID XBB.1.5 during pregnancy. Women who are vaccinated with NUVAXOVID XBB.1.5 during pregnancy are encouraged to enroll in the registry by visiting https://c-viper.pregistry.com/.

7.1.2 Breast-feeding

It is unknown if NUVAXOVID XBB.1.5 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 NUVAXOVID XBB.1.5 in children and adolescents less than 12 years of age have not yet been established.

7.1.4 Geriatrics

Clinical studies of NUVAXOVID include participants 65 years of age and older and their data contribute to the overall assessment of safety and effectiveness of NUVAXOVID XBB.1.5 (See 8 ADVERSE REACTIONS and 14 CLINICAL TRIALS sections).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Participants 18 Years of Age and Older

The safety of NUVAXOVID XBB.1.5 is inferred from the safety data of the NUVAXOVID (Original, Wuhan strain) vaccine, an investigational vaccine targeting the Omicron BA.1 variant (NVX-CoV2515), and an investigational vaccine targeting the Omicron BA.5 variant (NVX-CoV2540).

Investigational Vaccine NVX-CoV2515 targeting the Omicron Subvariant BA.1 of SARS-CoV-2

The safety, reactogenicity, and immunogenicity of a booster dose of NVX-CoV2515 was evaluated in an ongoing Phase 3 study in participants 18 to 64 years of age (2019nCoV-311 Part 1). In this study, 274 participants received a NUVAXOVID (Original, Wuhan strain) booster dose and 286 received a NVX-CoV2515 booster dose.

The overall safety profile for the Omicron BA.1 booster dose was similar to that seen after the NUVAXOVID (Original, Wuhan strain) booster dose. The most frequent adverse reactions were injection site tenderness (64.0%), fatigue (40.6%), injection site pain (38.9%), headache (37.5%), myalgia (25.1%), and malaise (23.3%). No new adverse reactions were identified for the BA.1 booster dose.

Investigational Vaccine NVX-CoV2540 targeting the Omicron Subvariant BA.5 of SARS-CoV-2

The safety, reactogenicity, and immunogenicity of a booster dose of NVX-CoV2540 was evaluated in an ongoing Phase 3 study in participants 18 years of age and older (2019nCoV-311 Part 2). In this study, 251 participants received a NUVAXOVID (Original, Wuhan strain) booster dose and 254 received a NVX-CoV2540 booster dose.

The overall safety profile for the Omicron BA.5 booster dose was similar to that seen after the NUVAXOVID (Original, Wuhan strain) booster dose. The most frequent adverse reactions were injection site tenderness (55.6%), fatigue (38.5%) injection site pain (32.9%), headache (29.0%), myalgia (23.4%), and malaise (19.0%). No new adverse reactions were identified for the BA.5 booster dose.

Participants 12 Through 17 Years of Age

The safety of NUVAXOVID XBB.1.5 is inferred from the safety data of the NUVAXOVID (Original, Wuhan strain) vaccine administered as a primary series and booster dose in adolescents, as well as adult data from Study 2019nCoV-311 Part 1 and Part 2.

NUVAXOVID (Original, Wuhan strain)

Participants 18 Years of Age and Older

The safety profile of NUVAXOVID (Original, Wuhan strain) presented below for participants 18 years of age and older is based on data generated from an interim analysis of pooled data from 3 ongoing clinical trials conducted in the United Kingdom (Study 1), the United States and Mexico (Study 2) and South Africa (Study 3). At the time of the analysis, a total of 48,698 participants ≥ 18 years of age received at least one dose of NUVAXOVID (Original, Wuhan strain) (n=29,297) or placebo (n=19,401). At the time of vaccination, the median age of participants who received NUVAXOVID (Original, Wuhan strain) was 48 years (range 18 to 95 years): 84.1% of participants were between 18 and 64 years of age and 15.9% of participants were ≥ 65 years of age.

Of the pooled reactogenicity data, which includes participants ≥ 18 years of age who received at least one dose of NUVAXOVID (Original, Wuhan strain) (n=21,395) or placebo (n=12,197), the most frequent adverse reactions were injection site tenderness (68%), injection site pain (56%), fatigue (45%), myalgia (44%), headache (41%), malaise (35%), arthralgia (20%), and nausea or vomiting (11%). Adverse reactions were usually mild to moderate in severity with a median duration of ≤ 2 days for local events and ≤ 1 day for systemic events following vaccination.

Of the pooled data following the booster vaccination in adults, frequencies and severity (all grades) of solicited adverse events generally increased, with most events being mild to moderate in severity.

The safety of a booster dose of NUVAXOVID (Original, Wuhan strain) was evaluated in an ongoing Phase 3 multicenter, randomized, observer-blinded, placebo-controlled study (Study 2019nCoV-301). A total of 12,738 participants received an open-label booster dose of NUVAXOVID (Original, Wuhan strain) at least 6 months after the two doses of NUVAXOVID (Original, Wuhan strain) (0.5 mL 3 weeks apart) as the primary vaccination series. An additional 39 participants received a booster dose without completing the two dose primary series. The safety analysis included evaluation of solicited adverse reactions within 7 days after the booster dose for participants who completed the electronic diary (n=10,137).

The most frequent solicited adverse reactions were injection site tenderness (73%), injection site pain (61%), fatigue (53%), muscle pain (51%), headache (45%), malaise (40%) and joint pain (26%).

Participants 12 Through 17 Years of Age

In addition, the safety of NUVAXOVID (Original, Wuhan strain) was evaluated in adolescents in an interim analysis of the pediatric expansion portion of an ongoing Phase 3 placebo-controlled clinical trial conducted in the United States (Study 2019nCoV-301). Safety data was collected in 2,232 participants aged 12 through 17 years, with and without evidence of prior SARS-CoV-2 infection, who received at least one dose of NUVAXOVID (Original, Wuhan strain) (n=1,487) or placebo (n=745). Demographic characteristics were similar

among adolescent participants who received NUVAXOVID (Original, Wuhan strain) and those who received placebo, and were generally similar to the adult portion of this study with regard to gender, race and ethnicity among adolescents who received NUVAXOVID (Original, Wuhan strain). At the time of vaccination, the median age was 14 years (67.1% aged 12 to < 15 years; 32.9% aged 15 to < 18 years).

The most frequent adverse reactions in participants 12 years through 17 years of age were injection site tenderness (71%), injection site pain (67%), headache (63%), myalgia (57%), fatigue (54%), malaise (43%), nausea or vomiting (23%), arthralgia (19%), and pyrexia (17%).

The safety of a booster dose of NUVAXOVID (Original, Wuhan strain) was evaluated in an interim analysis of the pediatric expansion portion of an ongoing Phase 3 multicenter, randomized, observer-blinded, placebo-controlled study (Study 2019nCoV-301). A total of 2,122 participants received two doses of NUVAXOVID (Original, Wuhan strain) (0.5 mL 3 weeks apart) as the primary vaccination series. A total of 1,499 participants (blinded or unblinded to original treatment assignment) received an open-label booster dose of NUVAXOVID (Original, Wuhan strain) approximately 9 months after receiving Dose 2 of the primary series. The most frequent solicited adverse reactions were injection site tenderness (66%), injection site pain (65%), headache (63%), fatigue (57%), muscle pain (60%), malaise (45%), and nausea/vomiting (23%) with a median duration of 1 to 2 days following vaccination. No new safety concerns from the time of the booster dose administration through 28 days after administration were noted among participants.

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 vaccine. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse vaccine reactions in real-world use.

Adults 18 years of age and older

Investigational Vaccine NVX-CoV2515 targeting the Omicron Subvariant BA.1 of SARS-CoV-2

Solicited Local and Systemic Adverse Reactions

Local and systemic adverse reactions were solicited within 7 days following vaccination with NUVAXOVID (Original, Wuhan strain), the investigational monovalent vaccine (Omicron BA.1), or the investigational bivalent vaccine (Original and Omicron BA.1) using an electronic diary. The reported frequency and severity of solicited local and systemic adverse reactions are presented for participants 18 to 64 years of age in Table 2.

Table 2 Number and Percentage of Participants with Solicited Local and Systemic Adverse Reactions Starting within 7[a] Days After Booster Dose in Participants 18 to 64 Years of Age Who Received Primary Vaccination with Another Authorized or Approved COVID-19 Vaccine (Safety Analysis Set)[b]

Event	Investigational Vaccine NVX-CoV2515 (Omicron BA.1) N = 283	NUVAXOVID (Original, Wuhan strain) N = 272	Investigational Vaccine NVX-CoV2373/NVX-CoV2515 (Original and Omicron BA.1) N = 268
Local Adverse Reactions			
Pain/tenderness			
Any Grade	196 (69.3)	192 (70.6)	173 (64.6)
Grade 3[c,d]	5 (1.8)	1 (0.4)	2 (0.7)
Redness (erythema)			
Any Grade	7 (2.5)	3 (1.1)	3 (1.1)
Grade 3[e]	0	0	1 (0.4)
Swelling			
Any Grade	7 (2.5)	3 (1.1)	4 (1.5)
Systemic Adverse Reactions			
Fever			
Any Grade	5 (1.8)	2 (0.7)	1 (0.4)
Grade 3[f]	1 (0.4)	0	0
Grade 4[f]	1 (0.4)	0	0
Headache			
Any Grade	106 (37.5)	95 (34.9)	96 (35.8)
Grade 3[g]	1 (0.4)	3 (1.1)	1 (0.4)
Fatigue/malaise			
Any Grade	127 (44.9)	111 (40.8)	121 (45.1)
Grade 3[h]	15 (5.3)	8 (2.9)	7 (2.6)
Muscle pain (myalgia)			
Any Grade	71 (25.1)	66 (24.3)	64 (23.9)
Grade 3[h]	5 (1.8)	0	0
Joint pain (arthralgia)			
Any Grade	27 (9.5)	29 (10.7)	16 (6.0)
Grade 3[h]	2 (0.7)	0	1 (0.4)

Table 2 Number and Percentage of Participants with Solicited Local and Systemic Adverse Reactions Starting within 7[a] Days After Booster Dose in Participants 18 to 64 Years of Age Who Received Primary Vaccination with Another Authorized or Approved COVID-19 Vaccine (Safety Analysis Set)[b]

Nausea or vomiting			
Any Grade	21 (7.4)	19 (7.0)	23 (8.6)
Grade 3[i]	0	1 (0.4)	0

[a] 7 days included day of vaccination and the subsequent 6 days. Events were collected in the electronic diary (eDiary).

[b] Absence of rows for Grade 3 or Grade 4 adverse reactions indicates no events were reported.

[c] Grade 3 pain: Defined as any use of narcotic pain reliever or prevents daily activity.

[d] Grade 3 tenderness: Defined as significant discomfort at rest.

[e] Grade 3 redness (erythema): Defined as > 10 cm.

[f] Grade 3 fever: Defined as 39.0 to 40°C (102.1 to 104°F). Grade 4 fever: Defined as >40°C (>104°F).

[g] Grade 3 headache: Defined as significant; any use of narcotic pain reliever or prevents daily activity.

[h] Grade 3 fatigue/malaise, muscle pain (myalgia), joint pain (arthralgia): Defined as significant; prevents daily activity.

[i] Grade 3 nausea or vomiting: Defined as prevents daily activity or requires outpatient IV hydration.

Unsolicited Adverse Events, Serious Adverse Events and Other Adverse Events of Interest

Participants were monitored through 28 days after the booster dose for unsolicited adverse events. Data are available for 829 participants for non-serious unsolicited adverse events.

Additionally, data for serious adverse events and adverse events of interest are available for 829 participants until 01 September 2023 (median follow-up post booster 66 days).

Serious adverse events were reported by 3 participants (1.0%) in the monovalent vaccine (Omicron BA.1) group, 2 participants (0.7%) in the NUVAXOVID (Original, Wuhan strain) group, and 2 participants (0.7%) in the bivalent vaccine (Original and Omicron BA.1) group.

Investigational Vaccine NVX-CoV2540 targeting the Omicron Subvariant BA.5 of SARS-CoV-2

Solicited Local and Systemic Adverse Reactions

Local and systemic adverse reactions were solicited within 7 days following vaccination with NUVAXOVID (Original, Wuhan strain), the monovalent vaccine (Omicron BA.5), or the bivalent vaccine (Original and Omicron BA.5) using an electronic diary. The reported frequency and severity of solicited local and systemic adverse reactions are presented for participants 18 years of age and older in Table 3.

Table 3 Number and Percentage of Participants with Solicited Local and Systemic Adverse Reactions Starting within 7[a] Days After Booster Dose in Participants 18 Years of Age and Older Who Received Primary Vaccination with Another Authorized or Approved COVID-19 Vaccine (Safety Analysis Set)[b]

Event	Investigational Vaccine NVX-CoV2540 (Omicron BA.5) N = 252	NUVAXOVID (Original, Wuhan strain) N = 251	Investigational Vaccine NVX-CoV2373/NVX-CoV2540 (Original and Omicron BA.5) N = 259
Local Adverse Reactions			
Pain/tenderness			
Any Grade	153 (60.7)	166 (66.1)	169 (65.3)
Grade 3[c,d]	4 (1.6)	2 (0.8)	2 (0.8)
Redness (erythema)			
Any Grade	5 (2.0)	8 (3.2)	6 (2.3)
Swelling			
Any Grade	8 (3.2)	6 (2.4)	6 (2.3)
Systemic Adverse Reactions			
Fever			
Any Grade	2 (0.8)	2 (0.8)	4 (1.5)
Grade 3[e]	0	0	1 (0.4)
Headache			
Any Grade	73 (29.0)	73 (29.1)	74 (28.6)
Grade 3[f]	4 (1.6)	2 (0.8)	3 (1.2)
Fatigue/malaise			
Any Grade	106 (42.1)	103 (41.0)	97 (37.5)
Grade 3[g]	3 (1.2)	7 (2.8)	8 (3.1)
Muscle pain (myalgia)			
Any Grade	59 (23.4)	71 (28.3)	67 (25.9)
Grade 3[g]	1 (0.4)	2 (0.8)	2 (0.8)
Joint pain (arthralgia)			
Any Grade	18 (7.1)	20 (8.0)	19 (7.3)
Grade 3[g]	0	1 (0.4)	1 (0.4)

Table 3 Number and Percentage of Participants with Solicited Local and Systemic Adverse Reactions Starting within 7[a] Days After Booster Dose in Participants 18 Years of Age and Older Who Received Primary Vaccination with Another Authorized or Approved COVID-19 Vaccine (Safety Analysis Set)[b]

Nausea or vomiting			
Any Grade	19 (7.5)	18 (7.2)	19 (7.3)
Grade 3[h]	1 (0.4)	0	0

[a] 7 days included day of vaccination and the subsequent 6 days. Events were collected in the electronic diary (eDiary).

[b] Absence of rows for Grade 3 or Grade 4 adverse reactions indicates no events were reported.

[c] Grade 3 pain: Defined as any use of narcotic pain reliever or prevents daily activity.

[d] Grade 3 tenderness: Defined as significant discomfort at rest.

[e] Grade 3 fever: Defined as 39.0 to 40°C (102.1 to 104°F).

[f] Grade 3 headache: Defined as significant; any use of narcotic pain reliever or prevents daily activity.

[g] Grade 3 fatigue/malaise, muscle pain (myalgia), joint pain (arthralgia): Defined as significant; prevents daily activity.

[h] Grade 3 nausea or vomiting: Defined as prevents daily activity or requires outpatient IV hydration.

Unsolicited Adverse Events

Serious Adverse Events and Other Adverse Events of Interest

Participants were monitored through 28 days after the booster dose for unsolicited adverse events. Data are available for 764 participants for non-serious unsolicited adverse events.

Additionally, data for serious adverse events and adverse events of interest are available for 764 participants until date May 31, 2023 (median follow-up post booster of 48 days).

Serious adverse events were reported by 4 participants (1.6%) in the monovalent vaccine (Omicron BA.5) group, 1 participant (0.4%) in the NUVAXOVID (Original, Wuhan strain) group, and 1 participant (0.4%) in the bivalent vaccine (Original and Omicron BA.5) group. Two participants, who received vaccine formulated with Omicron BA.5, reported adverse events of cranial nerve palsy, including a serious adverse event of fourth nerve cranial palsy with onset of symptoms 7 days post vaccination and a non-serious adverse event of sixth nerve palsy with onset of symptoms 14 days post vaccination. Both participants had predisposing risk factors, including diabetes, hypertension, hypercholesterolemia. The sixth nerve palsy was assessed as not related to vaccine. Currently available information on cranial palsies is insufficient to determine a causal relationship with the vaccine. The remaining serious adverse events were not related to vaccination.

NUVAXOVID (Original, Wuhan strain) Primary Series

Adults 18 years of age and older

The safety analysis of the pooled data was performed once the median follow-up duration of at least 2 months after vaccination was completed. The median duration of follow-up was 70 days post-Dose 2, with 32,993 (66%) participants completing more than 2 months follow-up. Participants are being monitored for adverse reactions through approximately 12 to 24 months after Dose 2.

When compared with Dose 1, local and systemic adverse reactions were more frequently reported after Dose 2.

Solicited Local and Systemic Adverse Reactions

The frequency and severity of solicited local and systemic reactions were collected within 7 days following each dose of NUVAXOVID (Original, Wuhan strain) or placebo in participants who recorded reactogenicity events in a diary in the pooled safety population.

The reported frequency and severity of solicited local reactions are presented by age group in Table 4 (18 to 64 years of age) and Table 5 (≥ 65 years of age).

Table 4: Frequency and Percentages of Participants with Solicited Local Adverse Reactions, by Maximum Severity, Within 7 Days of Each Dose – (Participants 18 to 64 Years of Age)

Solicited Local Adverse Reactions	NUVAXOVID (Original, Wuhan strain)		Placebo	
	Dose 1 N=18,871 n (%)	Dose 2 N=17,967 n (%)	Dose 1 N= 10,782 n (%)	Dose 2 N=10,173 n (%)
Tenderness (Grade ≥1)	9,571 (50.7)	12,444 (69.3)	1,656 (15.4)	1,460 (14.4)
Grade 3[c]	175 (0.9)	869 (4.8)	19 (0.2)	18 (0.2)
Grade 4[b]	1 (<0.1)	3 (<0.1)	1 (<0.1)	0 (0)
Pain (Grade ≥1)	6647 (35.2)	10361 (57.7)	1238 (11.5)	1294 (12.7)
Grade 3[a]	74 (0.4)	332 (1.9)	7 (0.1)	14 (0.1)
Grade 4[b]	0	5 (<0.1)	0	1 (<0.1)
Erythema (Grade ≥1)	184 (1.0)	1,130 (6.3)	30 (0.3)	30 (0.3)
Grade 3[d]	4 (<0.1)	139 (0.8)	1 (<0.1)	2 (<0.1)
Swelling (Grade ≥1)	163 (0.9)	1038 (5.8)	34 (0.3)	26 (0.3)
Grade 3[e]	6 (<0.1)	82 (0.5)	4 (<0.1)	1 (<0.1)

Source: pooled safety data from studies 2019nCoV-501, -301, -302 (excluding data from influenza vaccine substudy)

[a] Grade 3 pain: Defined as any use of narcotic pain reliever or prevents daily activity.

[b] Grade 4 pain, tenderness: Defined as Emergency Room (ER) visit or hospitalization.

[c] Grade 3 tenderness: Defined as significant discomfort at rest.

[d] Grade 3 erythema/redness: Defined as >10 cm.

[e] Grade 3 induration/swelling: Defined as >10 cm or prevents daily activity.

Table 5: Frequency and Percentages of Participants with Solicited Local Adverse Reactions, by Maximum Severity, Within 7 Days of Each Dose – (Participants ≥65 Years of Age)

Solicited Local Adverse Reactions	NUVAXOVID (Original, Wuhan strain)		Placebo	
	Dose 1 N=2,524 n (%)	Dose 2 N=2,292 n (%)	Dose 1 N=1,415 n (%)	Dose 2 N=1,261 n (%)
Tenderness (Grade ≥1)	833 (33.0)	1258 (54.9)	160 (11.3)	121 (9.6)
Grade 3[b]	11 (0.4)	35 (1.5)	2 (0.1)	1 (0.1)
Pain (Grade ≥1)	486 (19.3)	927 (40.5)	109 (7.7)	120 (9.5)
Grade 3[a]	4 (0.2)	14 (0.6)	1 (0.1)	1 (0.1)
Erythema (Grade ≥1)	20 (0.8)	120 (5.2)	5 (0.4)	4 (0.3)
Grade 3[c]	0 (0)	8 (0.4)	0 (0)	0 (0)
Swelling (Grade ≥1)	18 (0.7)	131 (5.7)	1 (0.1)	7 (0.6)
Grade 3[d]	1 (<0.1)	10 (0.4)	0 (0)	1 (0.1)

Source: pooled safety data from studies 2019nCoV-501, -301, -302 (excluding data from influenza vaccine substudy)

[a] Grade 3 pain: Defined as any use of narcotic pain reliever or prevents daily activity.

[b] Grade 3 tenderness: Defined as significant discomfort at rest.

[c] Grade 3 erythema/redness: Defined as >10 cm.

[d] Grade 3 induration/swelling: Defined as >10 cm or prevents daily activity.

The reported frequency and severity of solicited systemic reactions are presented in Table 6 (18 to 64 years of age) and Table 7 (≥65 years of age).

Table 6: Frequency and Percentages of Participants with Solicited Systemic Adverse Reactions, by Maximum Severity, Within 7 Days of Each Dose – (Participants 18 to 64 Years of Age)

Solicited Systemic Adverse Reactions	NUVAXOVID (Original, Wuhan strain)		Placebo	
	Dose 1 N=18,871 n (%)	Dose 2 N= 17,967 n (%)	Dose 1 N=10,782 n (%)	Dose 2 N=10,173 n (%)
Fatigue (Grade ≥1)	4,699 (24.9)	8,407 (46.8)	2,188 (20.3)	1,933 (19.0)
Grade 3[e]	228 (1.2)	1403 (7.8)	111 (1.0)	116 (1.1)
Grade 4[d]	4 (<0.1)	4 (<0.1)	1 (<0.1)	3 (<0.1)
Muscle pain (Grade ≥1)	4,289 (22.7)	8,267 (46.0)	1,362 (12.6)	1,090 (10.7)
Grade 3[e]	99 (0.5)	856 (4.8)	41 (0.4)	43 (0.4)
Grade 4[d]	3 (<0.1)	5 (<0.1)	2 (<0.1)	4 (<0.1)
Headache (Grade ≥1)	4,780 (25.3)	7,775 (43.3)	2,404 (22.3)	1,880 (18.5)
Grade 3[c]	155 (0.8)	548 (3.1)	81 (0.8)	63 (0.6)
Grade 4[d]	5 (<0.1)	5 (<0.1)	1 (<0.1)	2 (<0.1)

Table 6: Frequency and Percentages of Participants with Solicited Systemic Adverse Reactions, by Maximum Severity, Within 7 Days of Each Dose – (Participants 18 to 64 Years of Age)

Solicited Systemic Adverse Reactions	NUVAXOVID (Original, Wuhan strain)		Placebo	
	Dose 1 N=18,871 n (%)	Dose 2 N= 17,967 n (%)	Dose 1 N=10,782 n (%)	Dose 2 N=10,173 n (%)
Malaise (Grade ≥1)	2,701 (14.3)	6,623 (36.9)	1,148 (10.7)	1,086 (10.7)
Grade 3[e]	138 (0.7)	1073 (6.0)	60 (0.6)	65 (0.6)
Grade 4[d]	8 (<0.1)	9 (0.1)	2 (<0.1)	2 (<0.1)
Joint pain (Grade ≥1)	1,503 (8.0)	3,854 (21.5)	719 (6.7)	658 (6.5)
Grade 3[e]	64 (0.3)	436 (2.4)	30 (0.3)	31 (0.3)
Grade 4[d]	2 (<0.1)	5 (<0.1)	0 (0)	2 (<0.1)
Nausea or vomiting (Grade ≥1)	1,255 (6.7)	2,032 (11.3)	617 (5.7)	528 (5.2)
Grade 3[a]	21 (0.1)	39 (0.2)	14 (0.1)	13 (0.1)
Grade 4[b]	5 (<0.1)	7 (<0.1)	3 (<0.1)	2 (<0.1)
Fever (Grade ≥1)	107 (0.6)	1,023 (5.7)	72 (0.7)	48 (0.5)
Grade 3[f]	16 (0.1)	71 (0.4)	13 (0.1)	9 (0.1)
Grade 4[g]	6 (<0.1)	2 (<0.1)	1 (<0.1)	0 (0.)

Source: pooled safety data from studies 2019nCoV-501, -301, -302 (excluding data from influenza vaccine substudy)

[a] Grade 3 nausea/vomiting: Defined as prevents daily activity or requires outpatient intravenous hydration.

[b] Grade 4 nausea/vomiting: Defined as ER visit or hospitalization for hypotensive shock.

[c] Grade 3 headache: Defined as significant; any use of narcotic pain reliever or prevents daily activity.

[d] Grade 4 headache, fatigue/malaise, myalgia, arthralgia: Defined as ER visit or hospitalization.

[e] Grade 3 fatigue/malaise, myalgia, arthralgia: Defined as significant; prevents daily activity.

[f] Grade 3 fever: Defined as 39.0 to 40°C (102.1 to 104°F).

[g] Grade 4 fever: Defined as >40°C (>104°F).

Table 7: Frequency and Percentages of Participants with Solicited Systemic Adverse Reactions, by Maximum Severity, Within 7 Days of Each Dose – (Participants ≥65 Years of Age)

Solicited Systemic Adverse Reactions	NUVAXOVID (Original, Wuhan strain)		Placebo	
	Dose 1 N=2,524 n (%)	Dose 2 N=2,292 n (%)	Dose 1 N=1,415 n (%)	Dose 2 N=1,261 n (%)
Fatigue (Grade ≥1)	412 (16.3)	656 (28.6)	196 (13.9.)	175 (13.9)
Grade 3[d]	21 (0.8)	60 (2.6)	4 (0.3)	12 (1.0)
Muscle pain (Grade ≥1)	311 (12.3)	604 (26.4)	142 (10.0)	118 (9.4)
Grade 3[d]	3 (0.1)	32 (1.4)	4 (0.3)	3 (0.2)
Headache (Grade ≥1)	385 (15.3)	541 (23.6)	215 (15.2)	161 (12.8)
Grade 3[b]	13 (0.5)	17 (0.7)	4 (0.3)	2 (0.2)
Grade 4[c]	1 (<0.1)	1 (<0.1)	0 (0)	0 (0)

Table 7: Frequency and Percentages of Participants with Solicited Systemic Adverse Reactions, by Maximum Severity, Within 7 Days of Each Dose – (Participants ≥65 Years of Age)

Solicited Systemic Adverse Reactions	NUVAXOVID (Original, Wuhan strain)		Placebo	
	Dose 1 N=2,524 n (%)	Dose 2 N=2,292 n (%)	Dose 1 N=1,415 n (%)	Dose 2 N=1,261 n (%)
Malaise (Grade ≥1)	248 (9.8)	481 (21.0)	108 (7.6)	105 (8.3)
Grade 3[d]	12 (0.5)	38 (1.7)	3 (0.2)	5 (0.4)
Grade 4[c]	0 (0)	0 (0)	0 (0)	0 (0)
Joint pain (Grade ≥1)	155 (6.1)	287 (12.5)	89 (6.3)	71 (5.6)
Grade 3[d]	5 (0.2)	16 (0.7)	5 (0.4)	3 (0.2)
Grade 4[c]	0 (0)	1 (<0.1)	0 (0)	0 (0)
Fever (Grade ≥1)	13 (0.5)	44 (1.9)	9 (0.6)	11 (0.9)
Grade 3[e]	1 (<0.1)	3 (0.1)	0 (0)	2 (0.2)
Grade 4[f]	1 (<0.1)	0 (0)	0 (0)	0 (0)
Nausea or vomiting (Grade ≥1)	93 (3.7)	117 (5.1)	37 (2.6)	41 (3.3)
Grade 3[a]	0 (0)	2 (0.1)	0 (0)	0 (0)

Source: pooled safety data from studies 2019nCoV-501, -301, -302 (excluding data from influenza vaccine substudy)

[a] Grade 3 nausea/vomiting: Defined as prevents daily activity or requires outpatient intravenous hydration.

[b] Grade 3 headache: Defined as significant; any use of narcotic pain reliever or prevents daily activity.

[c] Grade 4 headache, malaise, arthralgia: Defined as ER visit or hospitalization.

[d] Grade 3 fatigue/malaise, myalgia, arthralgia: Defined as significant; prevents daily activity.

[e] Grade 3 fever: Defined as 39.0 to 40°C (102.1 to 104°F).

[f] Grade 4 fever: Defined as >40°C (>104°F).

Unsolicited Adverse Events

Across the pooled studies, participants were monitored for unsolicited adverse events after receipt of Dose 1 through 28 days after Dose 2 (49 days). The overall frequency of unsolicited adverse events for participants who received at least one dose of NUVAXOVID (Original, Wuhan strain) (n=29,297) or placebo (n=19,401) was 157 events per 100 person-years (e/100 PY) (18 to 64 years of age) and 153 e/100 PY (≥ 65 years of age) for those who received the vaccine and 133 e/100 PY (18 to 64 years of age) and 124 e/100 PY (≥ 65 years of age) for participants who received placebo.

Overall, the frequency of non-serious unsolicited adverse events was higher in the NUVAXOVID (Original, Wuhan strain) group than in placebo with events of fatigue, injection site pain, pyrexia, and myalgia occurring beyond the 7-day post-injection period largely accounting for the differences between the treatment groups. In addition, an imbalance of chills and pain in the extremity was reported. Chills occurred in 0.56% (n=165) of participants (N=29,297) who received NUVAXOVID (Original, Wuhan strain) and 0.10% (n=20) of participants (N=19,401) who received placebo. Pain in the extremity occurred in 1.46% (n=428) of participants who received NUVAXOVID (Original, Wuhan strain) and 0.37% (n=72) of participants who received placebo.

There were no other notable imbalances between treatment groups for unsolicited non-serious adverse events that would suggest a causal relationship to NUVAXOVID (Original, Wuhan strain).

Serious Adverse Events and Other Adverse Events of Interest

Participants were monitored for unsolicited serious adverse events and adverse events of interest, including but not limited to neurologic, inflammatory, vascular, and autoimmune disorders, from receipt of first vaccination through the respective data cut-off dates for each individual study within the pooled data analysis set. Serious adverse events and adverse events of special interest will continue to be recorded until the end of the studies, approximately 12 to 24 months after Dose 2 across the pooled clinical trials.

Serious adverse events (SAEs) across both treatment groups were uncommon (defined as ≥1/1,000 to <1/100), with a higher incidence rate in participants who receive placebo (4.09 events per 100 person-years) than in participants who received NUVAXOVID (Original, Wuhan strain) (3.82 events per 100 person-years). A slightly higher incidence rate occurred among participants ≥ 65 years of age. Incidence rates for SAEs in the younger age cohort (18 to 64 years) were 3.31 events per 100 person-years in NUVAXOVID (Original, Wuhan strain) participants and 3.59 events per 100 person-years in placebo participants. Incidence rates for SAEs in the older age cohort (≥ 65 years) was 6.69 events per 100 person-years in NUVAXOVID (Original, Wuhan strain) recipients and 6.65 events per 100 person-years in placebo recipients.

In the younger age cohort (18 to 64 years), there were no SAEs with an incidence rate greater than 0.10 events per 100 person-years in the NUVAXOVID (Original, Wuhan strain) group while 3 events, COVID-19 pneumonia (0.25), COVID-19 (0.23), and appendicitis (0.15) had incidence rates greater than 0.10 events per 100 person-years in the placebo group. In the older age cohort, SAEs that occurred at an incidence rate greater than 0.20 events per 100 person years in participants who received NUVAXOVID (Original, Wuhan strain) were COVID-19 (0.37) and prostate cancer (0.28) compared with pneumonia (0.51), COVID-19 (0.26), COVID 19 pneumonia (0.26), and atrial fibrillation (0.26) in the placebo group.

SAEs of cholecystitis, including acute cholecystitis, occurred with a higher incidence rate per 100 person-years in NUVAXOVID (Original, Wuhan strain) (0.11) than in placebo recipients (0.00), although the percentage of participants experiencing the event was infrequent (0.03%). All participants had a history of or a concurrent finding of cholelithiasis (gallstones) and most participants had additional risk factors including obesity and ≥ 40 years of age. Time to onset ranged from 6 to 64 days from the last dose of vaccine, with more than half of the events occurring more than 1 month following the last dose. All events resolved following cholecystectomy.

Myocarditis was identified in two teenage men shortly after receiving a second dose of vaccine resulting in a mild clinical course with complete resolution and no sequelae. Currently available information is insufficient to determine a causal relationship with the vaccine.

There were no other notable patterns of imbalance between treatment groups for specific categories of serious adverse events or adverse events of interest.

No deaths related to the vaccine were reported in the main and supportive clinical studies.

Adolescents 12 through 17 years of age

The safety analysis of NUVAXOVID (Original, Wuhan strain) in adolescents was performed once the median follow-up duration of at least 2 months after vaccination was completed. The median duration of follow-up was 71 days post Dose 2. Of the 1,468 participants who received both NUVAXOVID (Original, Wuhan strain) doses, 1,277 (87.0%) had at least 60 days of follow-up after their second vaccination.

Solicited Adverse Reactions

The reported number and percentage of the solicited local and systemic adverse reactions in participants 12 through 17 years of age are presented in Table 8 and Table 9 respectively.

Table 8: Frequency and Percentages of Adolescent Participants with Solicited Local Adverse Reactions, by Maximum Severity, Within 7 Days of Each Dose – (Participants 12 through 17 Years of Age)

Solicited Systemic Adverse Reactions	NUVAXOVID (Original, Wuhan strain)		Placebo	
	Dose 1 N=1,448 n (%)	Dose 2 N=1,394 n (%)	Dose 1 N=726 n (%)	Dose 2 N=686 n (%)
Tenderness (Grade ≥1)	817 (56.4)	909 (65.2)	153 (21.1)	97 (14.1)
Grade 3[a]	16 (1.1)	93 (6.7)	2 (0.3)	1 (0.1)
Pain (Grade ≥1)	646 (44.6)	850 (61.0)	126 (17.4)	102 (14.9)
Grade 3[b]	10 (0.7)	38 (2.7)	2 (0.3)	3 (0.4)
Erythema (Grade ≥1)	15 (1.0)	104 (7.5)	5 (0.7)	0
Grade 3[c]	0	10 (0.7)	0	0
Swelling (Grade ≥1)	20 (1.4)	111 (8.0)	3 (0.4)	1 (0.1)
Grade 3[d]	0	8 (0.6)	1 (0.1)	0

[a] Grade 3 tenderness: Defined as significant discomfort at rest.

[b] Grade 3 pain: Defined as any use of narcotic pain reliever or prevents daily activity.

[c] Grade 3 erythema/redness: Defined as >10 cm.

[d] Grade 3 induration/swelling: Defined as >10 cm or prevents daily activity.

Table 9: Frequency and Percentages of Adolescent Participants with Solicited Systemic Adverse Reactions, by Maximum Severity, Within 7 Days of Each Dose – (Participants 12 through 17 Years of Age)

Solicited Systemic Adverse Reactions	NUVAXOVID (Original, Wuhan strain)		Placebo	
	Dose 1 N=1,448 n (%)	Dose 2 N=1,394 n (%)	Dose 1 N=726 n (%)	Dose 2 N=686 n (%)
Fatigue (Grade ≥1)	350 (24.2)	695 (49.9)	112 (15.4)	100 (14.6)
Grade 3[a]	23 (1.6)	185 (13.3)	9 (1.2)	10 (1.5)
Muscle pain (Grade ≥1)	492 (34.0)	683 (49.0)	114 (15.7)	82 (12.0)
Grade 3[a]	17 (1.2)	104 (7.5)	4 (0.6)	6 (0.9)
Headache (Grade ≥1)	439(30.3)	793 (56.9)	181 (24.9)	119 (17.3)
Grade 3[b]	13 (0.9)	87 (6.2)	12 (1.7)	14 (2.0)
Grade 4[c]	0	1 (<0.1)	0	0
Malaise (Grade ≥1)	215 (14.8)	560 (40.2)	67 (9.2)	51 (7.4)
Grade 3[a]	16 (1.1)	126 (9.0)	7 (1.0)	4 (0.6)
Joint pain (Grade ≥1)	101 (7.0)	225 (16.1)	35 (4.8)	21 (3.1)
Grade 3[a]	6 (0.4)	40 (2.9)	1 (0.1)	2 (0.3)
Fever (Grade ≥1)	10(0.7)	235 (16.9)	4 (0.6)	1 (0.1)
Grade 3[d]	1 (<0.1)	31 (2.2)	0	0
Grade 4[e]	2 (0.1)	0	0	0
Nausea or vomiting (Grade ≥1)	112 (7.7)	277 (19.9)	54 (7.4)	33 (4.8)
Grade 3[f]	2 (0.1)	14 (1.0)	3 (0.4)	3 (0.4)
Grade 4[g]	0	1 (<0.1)	0	0

[a] Grade 3 fatigue/malaise, myalgia, arthralgia: Defined as significant; prevents daily activity.

[b] Grade 3 headache: Defined as significant; any use of narcotic pain reliever or prevents daily activity.

[c] Grade 4 headache: Defined as ER visit or hospitalization.

[d] Grade 3 fever: Defined as 39.0 to 40°C (102.1 to 104°F).

[e] Grade 4 fever: Defined as >40°C (>104°F).

[f] Grade 3 nausea/vomiting: Defined as prevents daily activity or requires outpatient intravenous hydration.

[g] Grade 4 nausea/vomiting: Defined as ER visit or hospitalization for hypotensive shock.

Unsolicited Adverse Reactions

For the safety analyses performed for the pediatric expansion portion of the main Phase 3 study, 2,232 adolescents aged 12 through 17 years of age (NUVAXOVID (Original, Wuhan strain); n=1,487; placebo, n=745) are being monitored for unsolicited adverse reactions through approximately 12 to 24 months after Dose 2.

The overall frequency of unsolicited adverse events was similar between the NUVAXOVID (Original, Wuhan strain) (16.3%) and placebo (15.8%) groups. Lymphadenopathy occurred in 0.7% (n=10) of adolescents who received NUVAXOVID (Original, Wuhan strain) and in 0% of adolescents who received placebo. There were no other notable patterns or numerical imbalances between treatment groups.

Serious Adverse Events

As of 06 October 2021, serious adverse events were reported in 0.5% (n=7) of adolescents who received NUVAXOVID (Original, Wuhan strain) and 0.3% (n=2) who received placebo. There were no notable patterns or imbalances between treatment groups for specific categories of serious adverse events that would suggest a causal relationship to NUVAXOVID (Original, Wuhan strain).

Booster Dose

Adults 18 Years of Age and Older

A booster dose of NUVAXOVID (Original, Wuhan strain) was evaluated in an ongoing Phase 2a/b randomized, placebo-controlled, observer-blinded clinical study conducted in South Africa (Study 2019nCoV-501), and an ongoing Phase 3, multi-centre, randomized, observer-blinded, placebo-controlled study in participants 18 years of age and older in the United States and Mexico (Study 2019nCoV-301). Solicited adverse reactions were reported within 7 days after the booster dose only in Study 2019nCoV-301 (Table 10 and Table 11), and unsolicited adverse reactions were reported in both Studies 2019nCoV-301 and Study 2019nCoV-501 through approximately 1 month after the booster dose. In Study 2019nCoV-301, safety was presented for two cohorts of participants; Cohort 1 participants received a booster dose of NUVAXOVID (Original, Wuhan strain) approximately 8 months after the second dose of the crossover primary series and Cohort 2 participants received a booster dose of NUVAXOVID (Original, Wuhan strain) approximately 11 months after the second dose of the initial primary series.

Table 10: Frequency and Percentages of Participants with Solicited Local Adverse Reactions, by Maximum Severity, Within 7 Days After a Booster Dose of NUVAXOVID (Original, Wuhan strain) – (Participants 19 to 79 Years of Age)

Solicited Local Adverse Reactions	NUVAXOVID Cohort 1 Booster Dose N=114 n (%)	NUVAXOVID Cohort 2 Booster Dose N=124 n (%)
Pain (Grade ≥ 1)	84 (73.7)	81 (65.3)
Grade 3[a]	1 (0.9)	4 (3.2)
Tenderness (Grade ≥ 1)	87 (76.3)	94 (75.8)
Grade 3[b]	7 (6.1)	10 (8.1)
Erythema (Grade ≥ 1)	7 (6.1)	8 (6.5)
Grade 3[c]	1 (0.9)	0
Swelling (Grade ≥ 1)	8 (7.0)	12 (9.7)
Grade 3[d]	1 (0.9)	1 (0.8)

Source: safety data from studies study 2019nCoV-301

[a] Grade 3 pain: Defined as any use of narcotic pain reliever or prevents daily activity.

[b] Grade 4 pain, tenderness: Defined as Emergency Room (ER) visit or hospitalization.

[c] Grade 3 tenderness: Defined as significant discomfort at rest.

[d] Grade 3 erythema/redness: Defined as >10 cm.

[e] Grade 3 induration/swelling: Defined as >10 cm or prevents daily activity.

Table 11: Frequency and Percentages of Participants with Solicited Systemic Adverse Reactions, by Maximum Severity, Within 7 Days of a Booster Dose – (Participants 19 to 79 Years of Age)

Solicited Systemic Adverse Reactions	NUVAXOVID (Original, Wuhan strain)	NUVAXOVID (Original, Wuhan strain)
	Cohort 1 Booster Dose N=114 n (%)	Cohort 2 Booster Dose N=124 n (%)
Nausea or vomiting (Grade ≥ 1)	13 (11.4)	22 (17.7)
Grade 3[a]	0	2 (1.6)
Grade 4[b]	0	1 (0.8)
Headache (Grade ≥ 1)	58 (50.9)	68 (54.8)
Grade 3[c]	5 (4.4)	9 (7.3)
Fatigue (Grade ≥ 1)	65 (57.0)	75 (60.5)
Grade 3[d]	16 (14.0)	23 (18.5)
Grade 4[e]	0	2 (1.6)
Malaise (Grade ≥ 1)	43 (37.7)	61 (49.2)
Grade 3[d]	11 (9.6)	16 (12.9)
Grade 4[e]	0	2 (1.6)
Muscle pain (Grade ≥ 1)	73 (64.0)	77 (62.1)
Grade 3[d]	8 (7.0)	12 (9.7)
Grade 4[e]	0	2 (1.6)
Joint pain (Grade ≥ 1)	31 (27.2)	41 (33.1)
Grade 3[d]	3 (2.6)	6 (4.8)
Fever (Grade ≥ 1)	7 (6.1)	8 (6.5)
Grade 3[f]	1 (0.9)	1 (0.8)

Source: safety data from studies study 2019nCoV-301

[a] Grade 3 nausea/vomiting: Defined as prevents daily activity or requires outpatient intravenous hydration.

[b] Grade 3 headache: Defined as significant; any use of narcotic pain reliever or prevents daily activity.

[c] Grade 4 headache, malaise, arthralgia: Defined as ER visit or hospitalization.

[d] Grade 3 fatigue/malaise, myalgia, arthralgia: Defined as significant; prevents daily activity.

[e] Grade 3 fever: Defined as 39.0 to 40°C (102.1 to 104°F).

[f] Grade 4 fever: Defined as >40°C (>104°F).

A review of the entire safety booster analysis set from study 2019nCoV-301 for participants who completed the electronic diary (N=10,137) demonstrates the overall frequency of solicited local and systemic adverse reactions after receipt of booster was similar to the frequency of solicited reactions following Dose 2 of the primary series. The severity of solicited reactions increased with each successive dose of vaccine administration.

Unsolicited Adverse Reactions

Across the pooled studies of 2019nCoV-301 and 2019nCoV-501, participants were monitored for unsolicited adverse events after receipt of booster through 28 days. Events considered treatment related included injection site pain (0.18%), injection site swelling (0.14%), injection site erythema (0.05%), injection site induration (0.05%), lymphadenopathy (0.05%), neuralgia (0.05%) vaccination site lymphadenopathy (0.05%), and vaccination site nodule (0.05%).

Unsolicited adverse events in the safety booster analysis set from study 2019nCoV-301 (N=12,777) following booster were infrequent and consistent with events reported following the primary series reflective of local and systemic type reactions.

Serious Adverse Reactions

In study 2019nCoV-301, through at least 28 days post-booster dose, serious adverse events in the ad-hoc booster analysis set (N=298) were reported in no participants in Cohort 1 and in 2 (1.3%) participants in Cohort 2. None of the serious adverse events were considered causally related to the use of NUVAXOVID (Original, Wuhan strain).

Serious adverse events in the safety booster analysis set from study 2019nCoV-301 (N=12777) were uncommon and consistent with the events reported following the primary series. Serious events of one case of pulmonary embolism and deep vein thrombosis, one case of acute myocardial infarction, and one case cellulitis were reported following booster administration.

A serious adverse event of extensive left leg and pelvic deep vein thrombosis and pulmonary embolism was reported 7 and 10 days, respectively, post booster administration of NUVAXOVID (Original, Wuhan strain) in a 35-year-old female participant receiving oral contraceptive therapy. Surgical intervention and thrombolytic therapy were required, and she requires prolonged anti-coagulation. Available information on these events is insufficient to determine a causal relationship with the vaccine.

A serious adverse event of a non-ST elevation myocardial infarction was reported in a 28-year-old male participant 3 days following booster administration of NUVAXOVID (Original, Wuhan strain). Clinical features were also consistent with myocarditis (chest pain and elevated troponin).

A serious adverse event of cellulitis of the injection site was reported in a 59-year-old male with onset 3 days after booster vaccination. The cellulitis resolved following antibiotic and steroid treatment. The event was considered related to the administration of NUVAXOVID (Original, Wuhan strain) based on the temporal relationship of the event and the known occurrence of injection site reactions, including swelling, pain, and erythema.

In study 2019nCoV-501, through at least 35 days post-booster dose, one serious adverse event was reported in 1 (<0.1%) participant. None of the serious adverse events were considered causally related to the use of NUVAXOVID (Original, Wuhan strain).

Adolescents 12 through 17 years of age

In an open-label portion of study 2019nCoV-301, 1,499 participants 12 through 17 years of age (based on enrolment until 16 June 2022) received a single booster dose of NUVAXOVID (Original, Wuhan strain) (0.5 mL) at least 5 months after the two-dose primary series (median of 9.0 months between completion of primary series and booster dose). Safety analyses included evaluation of solicited local and systemic adverse reactions within 7 days after a booster dose for participants who completed the electronic diary (n=190) and unsolicited adverse events within 28 days after a booster dose (n=220) in a subset of 220 participants who were included in the ad-hoc immunogenicity analysis. Safety analysis also included evaluation of serious adverse events and adverse events of interest after a booster dose (n=1,499) with a median follow-up of 135 days post booster dose through data extraction of 07 September 2022. The safety follow-up is ongoing.

Among the 1,499 boosted adolescent participants, 53.8% were male, 46.2% were female; 73.1% were White, 14.6% were Black or African American, 3.5% were Asian, 2.7% were American Indian (including Native Americans) or Alaskan Native, 0.3% were Native Hawaiian or Other Pacific Islander, and 5.1% were multiple races; 18.4% were Hispanic or Latino.

Solicited Adverse Reactions

Local and systemic adverse reactions were solicited within 7 days following the booster dose of NUVAXOVID (Original, Wuhan strain) using an electronic diary.

The reported frequency and severity of solicited local and systemic adverse reactions of participants 12 years through 17 years of age who received the booster dose and completed at least one day of the post-booster dose reactogenicity diary are presented in Table 12.

Table 12: Number and Percentage of Participants with Solicited Local and Systemic Adverse Reactions Starting within 7[a] Days After Booster Dose in Participants 12 Years Through 17 Years of Age (Booster Safety Analysis Set [b]) [c])

Event	NUVAXOVID (Original, Wuhan strain) N = 1249 n (%)
Local Adverse Reactions	
Pain/tenderness	
Any Grade	964 (77.2)
Grade 3[d,e]	145 (11.6)
Grade 4 [f]	1 (< 0.1)
Redness (erythema)	
Any Grade	130 (10.4)
Grade 3[g]	31 (2.5)
Swelling	
Any Grade	119 (9.5)
Grade 3[h]	20 (1.6)

Table 12: Number and Percentage of Participants with Solicited Local and Systemic Adverse Reactions Starting within 7[a] Days After Booster Dose in Participants 12 Years Through 17 Years of Age (Booster Safety Analysis Set [b]) [c])

Event	NUVAXOVID (Original, Wuhan strain) N = 1249 n (%)
Systemic Adverse Reactions	
Fever	
Any Grade	211 (16.9)
Grade 3[i]	44 (3.5)
Grade 4[f]	3 (0.2)
Headache	
Any Grade	788 (63.1)
Grade 3[j]	154 (12.3)
Grade 4[f]	2 (0.2)
Fatigue/malaise	
Any Grade	791 (63.3)
Grade 3[k]	264 (21.1)
Grade 4[f]	1 (< 0.1)
Muscle pain (myalgia)	
Any Grade	754 (60.4)
Grade 3[j]	143 (11.4)
Grade 4[f]	1 (< 0.1)
Joint pain (arthralgia)	
Any Grade	275 (22.0)
Grade 3[k]	50 (4.0)
Grade 4[f]	1 (< 0.1)
Nausea or vomiting	
Any Grade	292 (23.4)
Grade 3[l]	20 (1.6)

[a] 7 days included day of vaccination and the subsequent 6 days. Events and use of antipyretic or pain medication were collected in the electronic diary (eDiary).

[b] The analysis included a total of 1,249 participants who received the booster dose who completed their eDiary

[c] Absence of rows for Grade 4 adverse reactions indicates no events were reported.

[d] Grade 3 pain: Defined as any use of narcotic pain reliever or prevents daily activity.

[e] Grade 3 tenderness: Defined as significant discomfort at rest.

[f] Grade 4 for all reactions defined as ER visit or hospitalization

[g] Grade 3 redness (erythema): Defined as > 10 cm.

[h] Grade 3 swelling: Defined as > 10 cm or prevents daily activity.

[i] Grade 3 fever: Defined as 39.0 to 40°C (102.1 to 104°F).

[j] Grade 3 headache: Defined as significant; any use of narcotic pain reliever or prevents daily activity.

[k] Grade 3 fatigue/malaise, muscle pain (myalgia), joint pain (arthralgia): Defined as significant; prevents daily activity.

[l] Grade 3 nausea or vomiting: Defined as prevents daily activity, requires outpatient IV hydration.

Unsolicited Adverse Events (non-serious and serious)

In Study 2019nCoV-301, participants were monitored for non-serious unsolicited adverse events from the booster dose through 28 days after the booster dose and for serious adverse events for the duration of study participation. In the booster period, 1,499 adolescent participants received NUVAXOVID (Original, Wuhan strain). Of the participants who received the booster dose, 99% had a follow-up duration of at least 2 months (median 4.5 months) after the booster dose.

From the booster dose through 28 days after the booster dose, the overall frequency of adverse events in the subset of 220 participants was 5.0% with events of lymphadenopathy (n=2) and oropharyngeal pain (n=2) reported in more than 1 participant.

Serious adverse events in the boosted population of 1499 participants were reported by 3 (0.2%) participants who received a booster dose of NUVAXOVID (Original, Wuhan strain), with no events of myocarditis and/or pericarditis.

8.5 Post-Market Adverse Reactions

The following adverse reactions have been identified during post-authorization use of NUVAXOVID (Original, Wuhan strain).

Immune System Disorders: Anaphylaxis

Cardiac Disorders: Myocarditis and/or pericarditis (see 7 WARNINGS AND PRECAUTIONS)

Nervous System Disorders: Hypoaesthesia/paraesthesia

Ear and Labyrinth Disorders: Tinnitus

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.

9 DRUG INTERACTIONS

No interaction studies have been performed. Co-administration of NUVAXOVID (Original, Wuhan strain) with inactivated influenza vaccines has been evaluated in a limited number of adults (217 that received NUVAXOVID (Original, Wuhan strain) and 214 that received placebo) in an exploratory sub-study of 2019nCoV-302 (See 14 CLINICAL TRIALS sections). The binding antibody response to SARS-CoV-2 was 30% lower when NUVAXOVID (Original, Wuhan strain) was given concomitantly with inactivated influenza vaccine. The clinical significance of this is unknown.

Concomitant administration of NUVAXOVID XBB.1.5 with non-influenza vaccines has not been studied.

Do not mix NUVAXOVID XBB.1.5 with other vaccines/products in the same syringe.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

NUVAXOVID XBB.1.5 is composed of purified full-length SARS-CoV-2 recombinant spike (S) protein nanoparticle that is stabilized in its prefusion conformation. The addition of the saponin-based Matrix-M adjuvant facilitates activation of the cells of the innate immune system, which enhances the magnitude of the S protein-specific immune response. The two vaccine components elicit B- and T-cell immune responses to the S protein,including neutralizing antibodies, which may contribute to protection against COVID-19.

11 STORAGE, STABILITY AND DISPOSAL

Storage Prior to Use

The unopened NUVAXOVID XBB.1.5 multidose vials are stored refrigerated between 2° to 8°C (36° to 46°F) for a maximum of 12 months. Store in the original carton to protect from light.

Storage of Punctured vials

Chemical and physical in-use stability has been demonstrated from the time of first needle puncture to administration for 12 hours at 2°C to 8°C and for 6 hours at room temperature (up to 25°C).

NUVAXOVID XBB.1.5 does not contain a preservative. Store the opened vial between 2°C to 8°C for up to 12 hours or at room temperature (up to 25°C) for up to 6 hours after first puncture. (See 4.4 Administration for further discard details and instructions).

12 SPECIAL HANDLING INSTRUCTIONS

Store in a refrigerator (2°C to 8°C).

Do not freeze.

Keep the vials in the outer carton in order to protect from light.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Proper name: SARS-CoV-2 recombinant spike (rS) protein with Matrix-M adjuvant

Product Characteristics:

SARS-CoV-2 recombinant spike protein is produced in the *Spodoptera frugiperda* insect cell line infected with a baculovirus that encodes full-length, SARS-CoV-2 spike gene-producing trimeric spike proteins from the Omicron (XBB.1.5) strain. Matrix-M adjuvant contains *Quillaja saponaria* saponin fraction-A and *Quillaja saponaria* saponin fraction-C.

NUVAXOVID XBB.1.5 (COVID-19 Vaccine [Recombinant protein, Adjuvanted]) is a sterile, preservative-free, aqueous buffered suspension of the SARS-CoV-2 recombinant spike (rS) protein from the Omicron (XBB.1.5) strain that is co-formulated with Matrix-M adjuvant and a formulation buffer (See Table 1 for the full list of non-medicinal ingredients).

NUVAXOVID XBB.1.5 is a colourless to slightly yellow, clear to mildly opalescent suspension for intramuscular injection (pH 7.2). The vaccine is provided in a multidose vial containing 5 doses per vial. Each dose contains 5 mcg of SARS-CoV-2 recombinant spike protein with 50 mcg of Matrix-M adjuvant.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

The effectiveness of NUVAXOVID XBB.1.5 for individuals 12 years of age and older is inferred from studies which evaluated the primary series and booster vaccination with NUVAXOVID (Original, Wuhan strain) and supported by a study of a booster dose of an investigational vaccine targeting the Omicron BA.5 variant of SARS-CoV-2 in individuals 18 years of age and older, and by a study of a booster dose of an investigational vaccine targeting the Omicron BA.1 variant of SARS-CoV-2 in individuals 18 to 64 years of age.

Adults 18 Years of Age and Older

Study 4, Part 1 (2019nCoV-311 Part 1)

In Study 2019nCoV-311 Part 1, an observer-blind study conducted in Australia, a total of 831 randomized participants 18 to 64 years of age, who had previously received 3 doses of the Pfizer-BioNTech COVID-19 prototype Vaccine or the Moderna COVID-19 prototype vaccine were evaluated for immunogenicity received 1 of the following as a booster dose: NUVAXOVID (Original, Wuhan strain), investigational monovalent NVX-CoV2515 (targeting the Omicron BA.1 subvariant) or investigational bivalent vaccine NVX-CoV2373 + NVX-CoV2515. (NCT05372588)

The per-protocol analysis set included 119 participants in the NUVAXOVID (Original, Wuhan strain) vaccine group, 126 participants in the investigational monovalent NVX-CoV2515 vaccine group, and 118 participants in the bivalent vaccine NVX-CoV2373 + NVX-CoV2515 group. The median time since the last COVID-19

vaccination was 181.0 days, 178.0 days, and 182.5 days respectively. The median age of the population was 43.0 years (range 18-64); 306 (84.3%) participants were 18 through 54 years of age and 57 (15.7%) were 55 years and older. Overall, 41.6% were male, 58.4% were female, 0.8% were Hispanic or Latino, 84.3% were White, 0.6% were African American, 0.3% were Aboriginal Australian, 12.7% were Asian, 0.3% were Native Hawaiian or Pacific Islander, 0.6% were other races, and 1.4% were Multiracial. Demographic characteristics were similar across the three groups. Safety analysis included a median follow-up of 66 days post booster dose through data cutoff date of 01 September 2022. The safety follow-up is ongoing.

Study 4, Part 2 (2019nCoV-311 Part 2)

In study 2019nCoV-311 Part 2, a total of 694 participants 18 years of age and older, who were evaluated for immunogenicity and previously received 3 or more doses of the Pfizer-BioNTech COVID-19 Vaccine or the Moderna COVID-19 vaccine received 1 of the following as a booster dose: NUVAXOVID (Original, Wuhan strain), investigational monovalent vaccine NVX-CoV2540 (Omicron BA.5) or investigational bivalent vaccine NVX-CoV2373 + NVX-CoV2540 (Original and Omicron BA.5). The booster doses were administered a median of 12.8, 10.9, and 11.8 months after the last vaccination, respectively. GMRs and seroresponse rates were evaluated at 1 month after vaccination. (NCT05372588, Part 2 in Australia)

The per-protocol immunogenicity analysis set included 227 participants in the prototype vaccine group, 236 participants in the investigational monovalent BA.5 group and 231 participants in the investigational bivalent vaccine (Original and Omicron BA.5) group. The median time since the last COVID-19 vaccination was 347.0 days. The median age of the population was 43.0 years (range 18-75); 576 (83.0%) participants were 18 through 54 years of age and 118 (17.0%) were 55 years and older. Overall, 45.1% were male, 54.9% were female, 2.0% were Hispanic or Latino, 80.3% were White, 0.3% were African American, 1.9% were Aboriginal Australian, 12.5% were Asian, 0.7% were Native Hawaiian or Pacific Islander, 3.2% were other races, and 0.9% were Multiracial. Demographic characteristics were similar across the three groups. Following the booster dose through the cutoff date of 31 May 2023, the median follow-up time was 48.0 days.

Study 1 (2019nCoV-301)

Study 1 is an ongoing Phase 3, multi-centre, randomized, observer-blinded, placebo-controlled adult main study conducted in participants 18 years of age and older in the United States and Mexico and a pediatric expansion occurring in participants 12 through 17 years of age in the United States.

Participants 18 years of age and older

Upon enrolment in the adult main study, participants were stratified by age (18 to 64 years and ≥65 years) and assigned in a 2:1 ratio to receive NUVAXOVID (Original, Wuhan strain) or placebo. The study excluded participants who were significantly immunocompromised due to immunodeficiency disease; active cancer on chemotherapy; received chronic immunosuppressive therapy or received immunoglobulin or blood-derived products within 90 days; were pregnant; or had a history of laboratory-confirmed diagnosed COVID-19. Participants with clinically stable underlying co-morbidity were included as were participants with well-controlled human immunodeficiency virus (HIV) infection. Enrolment of adults completed in February 2021; safety and efficacy events were evaluated until each participant's first blinded crossover vaccination or as of

the data cut-off date of 31 May 2021. Participants will be followed for up to 24 months after the second dose for assessments of safety, and efficacy against COVID-19.

No less than 6 months after completion of the second dose of the primary vaccination series (initial or crossover) with NUVAXOVID (Original, Wuhan strain), participants who remained in the study (United States only) received a booster dose of NUVAXOVID (Original, Wuhan strain) in an open-label manner. Approximately half of the participants received a booster dose of NUVAXOVID (Original, Wuhan strain) approximately 8 months after the second dose of the crossover primary series (Cohort 1) and approximately half of the participants received a booster dose approximately 11 months after the second dose of the initial primary series (Cohort 2). Booster dosing was initiated on 13 December 2021, with enrolment completed on 12 May 2022. Immunogenicity and safety data were collected from 298 participants immediately prior to booster vaccination through 28 days after booster vaccination based on data cut-off date of 15 March 2022.

Demographic and baseline characteristics were balanced amongst participants who received NUVAXOVID (Original, Wuhan strain) and those who received placebo. Of the 29,949 participants randomized, 15.1% of participants in the vaccine group and 23.3% of participants in the placebo group requested unblinding to receive an authorized COVID-19 vaccine. In the Per-Protocol Efficacy (PP-EFF) analysis set for participants who received NUVAXOVID (Original, Wuhan strain) (n=17,312), which included all participants who received the full prescribed regimen of trial vaccine, had no exclusionary protocol deviations, and did not have evidence of SARS-CoV-2 infection through 6 days after the second dose, the median age was 47 years (range: 18 to 95 years); 88% (n=15,264) were 18 to 64 years old and 12% (n=2,048) were aged 65 and older; 48% were female; 94% were from the United States and 6% were from Mexico; 76% were White, 11% were Black or African American, 6% were American Indian (including Native Americans) or Alaskan Native, and 4% were Asian; 22% were Hispanic or Latino. At least one pre-existing comorbidity or lifestyle characteristic associated with an increased risk of severe COVID-19 was present in 16,493 (95%) participants. Comorbidities included: obesity (body mass index (BMI) ≥30 kg/m^2); chronic lung disease; diabetes mellitus type 2, cardiovascular disease; chronic kidney disease; or HIV. Other high-risk characteristics included age ≥65 years (with or without comorbidities) or age <65 years with comorbidities and/or living or working conditions involving known frequent exposure to SARS-CoV-2 or to densely populated circumstances.

Study 2 (2019nCoV-302)

Study 2 is an ongoing Phase 3, multi-centre, randomized, observer-blinded, placebo-controlled study in participants 18 to 84 years of age in the United Kingdom. Upon enrolment, participants were stratified by age (18 to 64 years; 65 to 84 years) and assigned in a 1:1 ratio to receive NUVAXOVID (Original, Wuhan strain) or placebo. The study excluded participants who were significantly immunocompromised due to immunodeficiency disease; current diagnosis or treatment for cancer; autoimmune disease/condition; received chronic immunosuppressive therapy or received immunoglobulin or blood-derived products within 90 days; bleeding disorder or continuous use of anticoagulants; history of allergic reactions and/or anaphylaxis; were pregnant; or had a history of laboratory -confirmed diagnosed COVID-19. Participants with clinically stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 4 weeks before enrolment were included, as were participants with known stable infection with HIV, hepatitis C virus (HCV), or hepatitis B virus (HBV).

Enrolment was completed in November 2020; data cut-off dates for efficacy and safety were 29 January 2021 and 23 February 2021, respectively. Participants are being followed for up to 12 months after the last vaccination for assessments of safety and efficacy against COVID-19.

Demographic and baseline characteristics were balanced amongst participants who received NUVAXOVID (Original, Wuhan strain) and participants who received placebo. Of the 15,187 participants randomized, 33.8% of participants in the vaccine group and 35.4% of participants in the placebo group requested to receive an authorized COVID-19 vaccine. In the Per-Protocol Efficacy (PP-EFF) analysis set for participants who received NUVAXOVID (Original, Wuhan strain) (n=7,020), which included all participants who received the full prescribed regimen of trial vaccine, had no exclusionary protocol deviations, and did not have evidence of SARS-CoV-2 infection through 6 days after the second dose, the median age (range) was 56 years (range: 18 to 84 years); 72% (n=5,067) were 18 to 64 years old and 28% (n=1,953) were aged 65 to 84; 49% were female; 95% were White; 3% were Asian; 1.0% were multiple races, 0.4% were Black or African American; 1% were Hispanic or Latino; and 45% had at least one comorbid condition.

Study 3 (2019nCoV-501)

Study 3 is an ongoing Phase 2a/b randomized, observer-blinded, placebo-controlled study in healthy HIV-negative participants 18 to 84 years of age and medically stable people living with HIV (PLWH) 18 to 64 years of age in South Africa. Upon enrolment, participants were assigned in a 1:1 ratio to receive NUVAXOVID (Original, Wuhan strain) or placebo. The study excluded participants who were significantly immunocompromised due to immunodeficiency disease; active cancer (malignancy) within 3 years; autoimmune disease/condition; received chronic immunosuppressive therapy or received immunoglobulin or blood-derived products within 90 days (excluding HAART in PLWH); bleeding disorder or continuous use of anticoagulants; history of allergic reactions and/or anaphylaxis; were pregnant; or had a history of laboratory confirmed diagnosed COVID-19. Participants with clinically stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 2 months before enrolment were included. Enrolment was completed in November 2020; data cut-off dates for efficacy and safety were 18 January 2021 and 23 February 2021, respectively. Participants are being followed for up to 12 months after the last vaccination for assessments of safety and efficacy against COVID-19.

Approximately 6 months after completion of the second dose of the primary series vaccination with NUVAXOVID (Original, Wuhan strain), participants who remained in the study received a booster dose of NUVAXOVID (Original, Wuhan strain) in a blinded manner. Booster dosing was initiated on 26 March 2021, with enrolment completed on 04 May 2021. Immunogenicity and safety data were collected from 1,898 participants immediately prior to booster vaccination through 35 days after booster vaccination based on a data cut-off date of 15 September 2021.

Demographic and baseline characteristics were balanced amongst participants who received NUVAXOVID (Original, Wuhan strain) and participants who received placebo. Of the 4,408 participants who received at least one dose of NUVAXOVID (Original, Wuhan strain) or placebo, the median age (range) was 28 years (range: 18 to 84 years); 94% (n=4,164) were HIV-negative and 6% (n=244) were PLWH; 96% (n=4,224) were 18 to 64 years old and 4% (n=184) were aged 65 to 84; 43% were female; 95% were Black or African American; 3% were White; 1% were Asian; 2% were multiple races, 2% were Hispanic or Latino; and 23% had at least one comorbid condition.

Adolescents 12 through 17 Years of Age

Study 1 (2019nCoV-301)

Study 1 is an ongoing Phase 3, multi-centre, randomized, observer-blinded, placebo-controlled study initially in adults (see above) with a subsequent pediatric expansion occurring in participants 12 through 17 years of age in the United States.

Upon enrolment in the pediatric expansion phase of Study 1, participants were randomized in a 2:1 ratio to receive NUVAXOVID (Original, Wuhan strain) or placebo without any stratification factors including age. The study excluded participants using the same criteria used in the adult phase of the same study. Enrolment of adolescents was completed in June 2021; safety, immunogenicity and efficacy events were evaluated until each participant's first blinded crossover vaccination (described below) or as of 06 October 2021 (data extraction date). Participants will be followed for up to 24 months after the second dose for assessments of safety, immunogenicity and efficacy against COVID-19. Following collection of sufficient safety data to support an interim order application, initial adolescent recipients of placebo were invited to receive two injections of NUVAXOVID (Original, Wuhan strain) given 21 days apart and initial recipients of NUVAXOVID (Original, Wuhan strain) to receive two injections of placebo 21 days apart ("blinded crossover"). All participants were offered the opportunity to continue to be followed in the study.

No less than 5 months after completion of the second dose of the primary vaccination series (initial or crossover) with NUVAXOVID (Original, Wuhan strain), participants who remained in the study (United States only) received a booster dose of NUVAXOVID (Original, Wuhan strain) in an open-label manner. Immunogenicity and safety data were collected from 220 participants immediately prior to the booster vaccination through 28 days after booster vaccination based on data cut-off date of 07 September 2022.

Demographic and baseline characteristics were balanced amongst participants who received NUVAXOVID (Original, Wuhan strain) and those who received placebo. Of the 2,247 participants randomized, 4.0% of participants in the vaccine group and 5.3% of participants in the placebo group requested unblinding to receive an authorized COVID-19 vaccine. In the Safety Analysis Set (SAS) for participants who received at least one dose of NUVAXOVID (Original, Wuhan strain) (n=1,487) or placebo (n=745), the median age was 14.0 years with an age distribution skewed to younger ages due to availability of an authorized COVID-19 vaccine for participants 16 years and older during the implementation of this study. The age distribution of participants was balanced between NUVAXOVID (Original, Wuhan strain) and placebo recipients with 67.1% in the total group (12 to 14 years of age) and 32.9% in the total group (15 to 17 years of age). Of all participants, 47.5% were female; 74.4% were White, 13.9% were Black or African American, 2.1% were American Indian or Alaska Native, 3.4% were Asian with the remainder of Mixed Origin or other categories; 18.5% were of Hispanic or Latino ethnicity. The majority of all subjects (53.2%) in the SAS had a normal BMI (18.0-24.9 kg/m^2) but 16.9% were overweight (BMI of 25.0-29.9 kg/m^2) and 26.8% obese (BMI of ≥ 30.0 kg/m^2). No other clinically relevant comorbidities were described in the adolescent phase of this study.

14.2 Study Results

Investigational Vaccine NVX-CoV2515 targeting the Omicron subvariant BA.1 of SARS-CoV-2 administered as a heterologous booster dose

Study 4 (2019nCoV-311 Part 1)

The co-primary objectives of the study were to demonstrate the superiority of the investigational vaccine NVX-CoV2515 compared to NUVAXOVID (Original, Wuhan strain) in inducing neutralizing antibodies (MN50) to the Omicron BA.1 subvariant virus at Day 14 and to demonstrate non inferiority of the investigational vaccine NVX-CoV2515 compared to NUVAXOVID (Original, Wuhan strain) for the difference in SRRs in participants previously vaccinated with 3 doses of the Moderna and/or Pfizer-BioNTech prototype COVID-19 vaccines. Neutralizing antibody titers were evaluated 14 days after vaccination for the original Wuhan virus using a validated live virus microneutralization assay [MN50] and for the Omicron BA.1 subvariant virus, using a partially validated live virus microneutralization assay [MN50]. Participants included in the day 14 per protocol analysis set population (n=240) had no serologic or virologic evidence of SARS-CoV-2 infection prior to the booster dose.

The first primary endpoint was achieved as the investigational vaccine NVX-CoV2515 induced a superior response in MN50 GMT versus NUVAXOVID (Original, Wuhan strain) against the Omicron BA.1 subvariant virus (130.8 vs 83.9, respectively) using a validated assay at Day 14, with a GMT ratio of 1.6 (95% CI: 1.33, 2.03) and a lower bound of the two-sided 95% CI > 1 (1.33) (Table 13).

The second primary endpoint was achieved as the investigational vaccine NVX CoV2515 induced a non-inferior SRR against the Omicron BA.1 subvariant virus versus NUVAXOVID (Original, Wuhan strain) (73.4% vs 50.9%, respectively) at Day 14, with a difference in SRRs of 22.5% (95% CI: 10.3, 34.2) and a lower bound of the two-sided 95% CI > -5% (10.3%) (Table 14).

Table 13: Summary of Geometric Mean Titers of Investigational Vaccine NVX-CoV2515 Against the Omicron BA.1 Virus at 14 Days After a Booster Dose Versus NUVAXOVID (Original, Wuhan strain) at 14 Days After a Booster Dose, Participants 18 to 64 Years of Age, PP Analysis Set[1]

Investigational Vaccine NVX-CoV2515 (N = 124)[2] GMT (95% CI)[3]	NUVAXOVID (Original, Wuhan strain) (N = 116)[2] GMT (95% CI)[3]	GMT Ratio[4] Investigational Vaccine NVX-CoV2515 /NUVAXOVID (Original, Wuhan strain) (95% CI)[4]	Met Success Criterion
130.8 (109.2, 156.7)	83.9 (69.6, 101.2)	1.6 (1.33, 2.03)	Yes[5]

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; GMT = geometric mean titer; MN_{50} = microneutralization assay with an inhibitory concentration of 50%; PP = Per-Protocol; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

[1] PP Analysis Set included participants who received study vaccine according to protocol, did not have serologic or virologic evidence of SARS-CoV-2 infection on or before the booster dose, and had no major protocol violations that were considered clinically relevant to impact immunogenicity.

[2] The analysis included participants of the PP analysis set who had immunogenicity data available at baseline and at 14 days post booster dose.

[3] The 95% CI for GMT were calculated based on the t-distribution of the log-transformed values, then back transformed to the original scale for presentation.

[4] An ANCOVA with vaccine group as fixed effect and baseline value as covariate was performed to estimate the GMT ratio. The mean difference between vaccine groups and the corresponding CI limits was then exponentiated to obtain the ratio of MN_{50} GMTs and the corresponding 95% CIs.

[5] Success criterion is met if the lower bound of the two-sided 95% CI was above unity (ie, > 1).

Table 14: Summary of Seroresponse Rate of Investigational Vaccine NVX-CoV2515) Against the Omicron BA.1 Virus at 14 Days After a Booster Dose Versus NUVAXOVID (Original, Wuhan strain) at 14 Days After a Booster Dose, Participants 18 to 64 Years of Age, PP Analysis Set1

Investigational Vaccine NVX-CoV2515 (N = 124)[2] SRR[3] % (95% CI)[4]	NUVAXOVID (Original, Wuhan strain) (N = 116)[2] SRR[3] % (95% CI)[4]	Difference in SRR Investigational Vaccine NVX-CoV2515 - NUVAXOVID (Original, Wuhan strain) % (95% CI)[5]	Met Success Criterion
73.4 (64.7, 80.9)	50.9 (41.4, 60.3)	22.5 (10.3, 34.2)	Yes[6]

Abbreviations: CI = confidence interval; MN_{50} = microneutralization assay with an inhibitory concentration of 50%; PP = Per-Protocol; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SRR = seroresponse rate.

[1] PP Analysis Set included participants who received study vaccine according to protocol, did not have serologic or virologic evidence of SARS-CoV-2 infection on or before the booster dose, and had no major protocol violations that were considered clinically relevant to impact immunogenicity.

[2] The analysis included participants of the PP analysis set who had immunogenicity data available at baseline and at 14 days post booster dose.

[3] The SRR was defined as percentage of participants at each post vaccination visit with a titer ≥ 4-fold rise in MN_{50} level from baseline (before the first dose of the study vaccine).

[4] The 95% CI for SRR was calculated using the exact Clopper-Pearson method.

[5] The 95% CI for the difference in SRR was calculated based on the method of Miettinen and Nurminen.

[6] Success criterion is met if the lower bound of the two-sided 95% CI for the percentage difference was above -5%.

In sensitivity analyses using a per protocol analysis set that did not exclude participants with serologic evidence of SARS-CoV-2 infection (PP2 Analysis Subset, n= 491), neutralizing antibody responses against the Omicron BA.1 virus induced by the investigational monovalent NVX-CoV2515 vaccine were compared with neutralizing antibody responses against the Omicron BA.1 virus induced by the NUVAXOVID (Original, Wuhan strain) vaccine 14 days after study vaccination.

The GMTs were 318.2 (95% CI: 269.8, 375.3) in the NVX-CoV2515 group (n= 247) and 218.1 (95% CI: 186.0, 255.7) in the NUVAXOVID group (n= 244), resulting in an estimated GMT ratio of the investigational monovalent NVX-CoV2515 vaccine versus the NUVAXOVID (Original, Wuhan strain) vaccine of 1.5 (95% CI: 1.36, 1.77).

The seroresponse rates (percentage) were 54.3% in the monovalent NVX-CoV2515 vaccine group and 32.0% in the NUVAXOVID (Original, Wuhan strain) vaccine, resulting in a difference in seroresponse rates (percentage) of 22.3% (95% CIs: 13.6%, 30.6%).

Investigational Vaccine NVX-CoV2540 targeting the Omicron subvariant BA.5 of SARS-CoV-2 administered as a heterologous booster dose

Study 4 (2019nCoV-311 Part 2)

As an exploratory endpoint, neutralizing antibody responses induced by a monovalent investigational vaccine NVX-CoV2540 targeting the Omicron BA.5 subvariant administered as a booster dose in individuals 18 years of age and older who previously received 3 or more doses of the Pfizer-BioNTech COVID-19 Vaccine or the Moderna COVID-19 vaccine were evaluated. Neutralizing antibody titers against a pseudovirus expressing the SARS-CoV-2 Spike protein from the Omicron BA.5 virus, measured by a validated pseudovirus neutralization assay [ID50], were evaluated at 28 days after vaccination. Participants included in the day 28 per protocol analysis set population (n=467) had no virologic evidence of SARS-CoV-2 infection at time of the booster dose. The NVX-CoV2540 investigational vaccine would have met all three of the study's success criteria for the co-primary endpoints compared to the NUVAXOVID (Original, Wuhan strain) vaccine demonstrating a superior neutralizing antibody titer for the Omicron BA.5 subvariant, a non-inferior SRR for the Omicron BA.5 subvariant and noninferior neutralizing antibody titer against the Original strain.

NUVAXOVID (Original, Wuhan strain)

Primary Series

Efficacy in Adults 18 Years of Age and Older After Two Doses

Study 1 (2019nCoV-301)

As of the cut-off date of 31 May 2021, the primary efficacy analysis population (referred to as the Per-Protocol Efficacy [PP-EFF] analysis set) included 25,452 participants who received either NUVAXOVID (Original, Wuhan strain) (n=17,312) or placebo (n=8,140), received two doses (Dose 1 on day 0; Dose 2 between days 21 to 28), did not experience an exclusionary protocol deviation, and did not have evidence of SARS-CoV-2 infection through 6 days after the second dose.

COVID-19 cases were confirmed by polymerase chain reaction (PCR) through a central laboratory. Vaccine efficacy overall and a subgroup analysis by age and by mild, moderate, or severe COVID-19 are presented in Table 15.

Table 15: Vaccine efficacy analyses of PCR-confirmed COVID-19 with onset from 7 days after second vaccination[a] - PP-EFF analysis set; Study 1 (2019nCoV-301)

Subgroup	NUVAXOVID (Original, Wuhan strain)			Placebo			% Vaccine Efficacy (95% CI)
	Participants N	COVID-19 cases n (%)	Incidence Rate Per Year Per 1,000 People[b]	Participants N	COVID-19 cases n (%)	Incidence Rate Per Year Per 1,000 People[b]	
Primary efficacy endpoint							
All participants	17,312	14 (0.1)	3.26	8,140	63 (0.8)	34.01	90.4% (82.9; 94.6)[c,d]
Mild	—	14 (0.1)	—	—	49 (0.6)	—	—
Moderate	—	0	—	—	10 (0.1)	—	—
Severe	—	0	—	—	4 (<0.1)	—	—
Subgroup analyses of the primary efficacy endpoint[e]							
18 to 64 years of age	15,264	12 (0.1)	4.60	7,194	61 (0.8)	54.11	91.5% (84.2, 95.4)[c]
≥ 65 years of age	2,048	2 (0.1)	5.69	946	2 (0.2)	13.37	57. 5% (-486.9, 96.9)[e]

[a]Vaccine efficacy evaluated in participants without major protocol deviations who were seronegative and PCR-negative to SARS-CoV-2 at baseline and do not have a laboratory confirmed current SARS-CoV-2 infection with symptom onset through 6 days after the second dose, and who have received the full prescribed regimen of trial vaccine.

[b]Mean disease incidence rate per year in 1,000 people.

[c]Based on log-linear model of PCR-confirmed COVID-19 infection incidence rate using Poisson regression with treatment group and age strata as fixed effects and robust error variance, where vaccine efficacy = 100 × (1 – relative risk).

[d]Met primary efficacy endpoint criterion for success with a lower bound confidence interval (LBCI) > 30%.

[e]For participants ≥65 years of age, the event rates were too low (two or fewer events) to allow meaningful interpretation.

Vaccine efficacy of NUVAXOVID (Original, Wuhan strain) to prevent the onset of COVID-19 from 7 days after Dose 2 was 90.40% (PP-EFF analysis set).

Study 2 (2019nCoV-302)

As of the cut-off date of 29 January 2021, the primary efficacy PP-EFF analysis set included 14,039 participants who received either NUVAXOVID (Original, Wuhan strain) (n= 7,020) or placebo (n= 7,019), received two doses (Dose 1 on day 0; Dose 2 between 21 and 28 days), did not experience an exclusionary protocol deviation, and did not have evidence of SARS-CoV-2 infection through 6 days after the second dose.

Vaccine efficacy overall and a subgroup analysis by age and by severity of COVID-19 are presented in Table 16.

Table 16: Vaccine efficacy analysis of PCR-confirmed COVID-19 with onset at least 7 days after the second vaccination[a] - PP-EFF analysis set: Study 2 (2019nCoV-302)

Subgroup	NUVAXOVID (Original, Wuhan strain)			Placebo			% Vaccine Efficacy (95% CI)
	Participants N	COVID-19 cases n (%)	Incidence Rate Per Year Per 1,000 People[b]	Participants N	COVID-19 cases n (%)	Incidence Rate Per Year Per 1,000 People[b]	
Primary efficacy endpoint							
All participants	7,020	10 (0.1)	6.53	7,019	96 (1.4)	63.43	89.7% (80.2, 94.6)[c,d]
Mild	—	1 (<0.1)	—	—	28 (0.4)	—	—
Moderate	—	9 (0.1)	—	—	63 (0.9)	—	—
Severe	—	0	—	—	5 (<0.1)	—	—
Subgroup analyses of the primary efficacy endpoint							
18 to 64 years of age	5,067	9 (0.2)	12.30	5,062	87 (1.7)	120.22	89.8%[c] (79.7, 94.9)
65 to 84 years of age	1,953	1 (0.10)	—	1,957	9 (0.9)	—	88.9%[e] (20.2, 99.7)

[a]Vaccine efficacy evaluated in participants without major protocol deviations who were seronegative and PCR-negative to SARS-CoV-2 at baseline and do not have a laboratory confirmed current SARS-CoV-2 infection with symptom onset through 6 days after the second dose, and who have received the full prescribed regimen of trial vaccine.

[b]Mean disease incidence rate per year in 1000 people.

[c]Based on Log-linear model of occurrence using modified Poisson regression with logarithmic link function, treatment group and strata (age-group and pooled region) as fixed effects and robust error variance.

[d]Met primary efficacy endpoint criterion for success with a lower bound confidence interval (LBCI) > 30%.

[e]Based on the Clopper-Pearson model (due to few events), 95% CIs calculated using the Clopper-Pearson exact binomial method adjusted for the total surveillance time.

Vaccine efficacy of NUVAXOVID (Original, Wuhan strain) to prevent the onset of COVID-19 from 7 days after Dose 2 was 89.7% (PP-EFF analysis set).

Immunogenicity and Efficacy in Adolescents 12 through 17 years of age

Study 1 (2019nCoV-301)

An analysis of the SARS-CoV-2 neutralizing antibody response 35 days after Dose 2 was conducted in a subset of adolescent participants 12 through 17 years of age and a subset of participants 18 through 25 years of age from the adult main study. Non-inferior immune responses as assessed by geometric mean titers and seroconversion rates were demonstrated in a comparison of adolescents 12 through 17 years of age to participants 18 through 25 years of age (Table 17).

Table 17: SARS-CoV-2 Neutralizing Antibody Geometric Mean Titer Ratio and Seroconversion Rate – Comparison of Adolescents 12 Years Through 17 Years of Age to Participants 18 Years Through 25 Years of Age – Per-Protocol Immunogenicity Analysis Set[a]

Assay	Time Point	12 Years Through 17 Years	18 Years Through 25 Years	12 Years Through 17 Years/ 18 Years Through 25 Years	
		GMT[b] (95% CI) n=390	**GMT[b] (95% CI) n=416**	**GMR[c] (95% CI)**	**Met Noninferiority Criteria[d]**
SARS-CoV-2 wild-type microneutralization assay (1/dilution)[e]	14 days after Dose 2	3,859.60 (3422.83, 4352.10)	2,633.55 (2388.60, 2903.62)	1.46 (1.25, 1.71)[d]	Yes
		SCR%[f] (95% CI) n=385	**SCR%[f] (95% CI) n=416**	**Difference in SCR%[g] (95% CI)**	
		98.72 (97.03, 99.58)	99.76 (98.67, 99.99)	-1.04 (-2.75, 0.20)	

CI = Confidence interval; GMR = Geometric mean ratio; GMT = Geometric mean titer; SCR = Seroconversion rate

[a] PP-IMM Analysis Set included participants who received two doses (0.5 mL 3 weeks apart) of NUVAXOVID (Original, Wuhan strain) in the initial vaccination period, had immunogenicity blood samples collected at Days 0 and 35, did not have serologic or virologic evidence of SARS-CoV-2 infection up to the Day 35 blood draw and without major protocol deviations through the Day 35 blood draw.

[b] The 95% CI for GMT is calculated based on the t-distribution of the log-transformed values, then back transformed to the original scale for presentation.

[c] GMR is defined as the ratio of two geometric mean titers for comparison of two age cohorts. An analysis of covariance (ANCOVA) with age cohort as main effect and baseline microneutralization assay neutralizing antibodies as covariate was performed to estimate the GMR.

[d] Noninferiority was achieved if the following 3 pre-specified criteria were met simultaneously: 1) Lower bound of two-sided 95% CI for the ratio of GMTs ($GMT_{12\text{-}17yo}/GMT_{18\text{-}25yo}$) > 0.67; 2) Point estimate of the ratio of GMTs ≥ 0.82; and 3) Lower bound of the two-sided 95% CI for difference of SCRs ($SCR_{12\text{-}17yo} - SCR_{18\text{-}25yo}$) was > -10%.

[e] Validated virus neutralizing assay (VNA) with wild-type virus (SARS-CoV-2 hCoV-19/Australia/VIC01/2020 [GenBank MT007544.1]; 360biolabs, Melbourne, Australia). The lower limit for quantification for this assay was a titer of 20, with titers below this level documented as 10.

[f] SCR is defined as percentage of participants with a ≥ 4-fold difference in titers between Day 35 and Day 0. The 95% CI for SCR was calculated using the Clopper-Pearson exact method.

[g] Difference in SCR in the adolescent primary series expansion (Study 1) for 12 years through 17 years of Study 1 minus SCR in Adult Main Study (Study 1) for 18 years through 25 years. The 95% CI for the difference of SCR between groups was calculated with the method of Miettinen and Nurminen.

A descriptive efficacy analysis evaluating PCR-confirmed COVID-19 cases was performed in 1,799 participants who were included in the per-protocol efficacy (PP-EFF) Analysis Set, which required receipt of two doses (Dose 1 on day 0; Dose 2 on day 21), no exclusionary protocol deviation(s), and no evidence of SARS-CoV-2 infection through 6 days after the second dose. COVID-19 was defined as first episode of PCR-confirmed mild, moderate, or severe COVID-19 with at least one or more of the predefined symptoms within each severity category. Mild COVID-19 was defined as fever, new onset cough or at least 2 or more additional COVID-19 symptoms. In the PP-EFF Analysis Set, 47.2% were female; 76.1% were White, 12.9% were Black or African American, 1.1% were American Indian or Alaska Native, 3.6% were Asian with the remainder of Mixed Origin or other categories; 15.8% were Hispanic or Latino ethnicity; median age of 14.0 years (range 12-17 years) and 25.3% were classified as obese as per BMI. The median interval between doses of study vaccine was 22 days (range 14-43 days).

As of 06 October 2021 (data extraction date), there were 20 cases of PCR-confirmed symptomatic mild COVID-19 (NUVAXOVID (Original, Wuhan strain); n=6 [0.5%]; placebo, n=14 [2.4%]) resulting in a point estimate of efficacy of 79.5% (95% CI: 46.8%, 92.1%) (Table 18). At the time of this analysis, the Delta (B.1.617.2 and AY lineages) variant of concern (VOC) was the predominant variant circulating in the US and accounted for all cases from which sequence data are available (11/20, 55%). As of the data extraction date, the PP-EFF Analysis Set had a median follow-up of 64 days following 7 days post-Dose 2 during the pre-crossover period.

Table 18: Vaccine Efficacy Against PCR-confirmed COVID-19 with Onset from 7 Days After Second Vaccination[a] (PP-EFF Analysis Set)

Subgroup	NUVAXOVID (Original, Wuhan strain)			Placebo			Vaccine Efficacy (95% CI) (%)
	Partici-pants N	COVID-19 Cases[c] n (%)	Mean Incidence Rate Per 100 Person-Years	Partici-pants N	COVID-19 Cases[c] n (%)	Mean Incidence Rate Per 100 Person-Years	
Primary efficacy endpoint							
All participants	1,205	6 (0.5)	2.90	594	14 (2.4)	14.20	79.54 (46.83, 92.13)[b]
Mild	—	6 (0.5)	—	—	14 (2.4)	—	—
Moderate	—	0	—	—	0	—	—
Severe	—	0	—	—	0	—	—

[a] Vaccine efficacy (VE) evaluated in participants without major protocol deviations who were seronegative (for SARS-CoV-2) at baseline and did not have a laboratory confirmed current SARS-CoV-2 infection with symptom onset through 6 days after the second dose, and who had received two doses of vaccine or placebo as randomized.

[b] Based on Modified Poisson regression with logarithmic link function and treatment group as fixed effect and robust error variance (Zou 2004).

[c] All cases for which sequence data are available (vaccine n=2; placebo n=7) were due to the Delta variant.

Booster Dose

Immunogenicity in Adults 18 Years of Age and Older

Study 1 (2019nCoV-301)

As of the cut-off date of 15 March 2022, the immunogenicity analysis population (referred to as the Per-Protocol Immunogenicity [PP-IMM] analysis set) included 243 participants who completed both doses of their primary series vaccination with NUVAXOVID (Original, Wuhan strain), received a single booster dose of NUVAXOVID (Original, Wuhan strain), completed Day 35 blood samples, did not have a positive nasal swab PCR or positive serum anti-nucleoprotein (NP) antibodies on or before the booster dose (if available), had not received an EUA vaccine and remained blinded to their original randomized treatment assignment during the primary series of vaccination. Of these participants, 117 received a single booster dose of NUVAXOVID (Original, Wuhan strain) approximately 8 months after the second dose of the crossover primary series vaccination (Cohort 1) and 126 received a single booster dose of NUVAXOVID (Original, Wuhan strain) approximately 11 months after the second dose of the initial primary series vaccination (Cohort 2). Immune

responses were measured by a microneutralization assay against SARS-CoV-2 wild-type virus (ancestral Wuhan strain) that defined the titer as the concentration that yielded >50% viral inhibition [MN50]. In both cohorts, a single booster dose of NUVAXOVID (Original, Wuhan strain) elicited robust MN50 responses at 28 days after booster administration with neutralizing antibody GMTs of 4,235.8 and 5,972.6 in Cohort 1 and Cohort 2, respectively, that were higher than those reported at 14 days after primary series vaccination with NUVAXOVID (Original, Wuhan strain) (1,162.3 and 1,914.3, respectively). The ratios of MN50 titers at 28 days post-booster dose versus at 14 days post-primary series vaccination were 3.7 (95% CI: 2.9 – 4.7) and 3.1 (95% CI: 2.5 – 4.0) for Cohort 1 and Cohort 2, respectively.

Study 3 (2019nCoV-501)

At the cut-off date of 15 September 2021, the PP-IMM analysis set included 623 HIV-negative participants who completed both doses of their primary series vaccination with NUVAXOVID (Original, Wuhan strain), received a single booster dose of NUVAXOVID (Original, Wuhan strain), had at least 1 baseline and 1 serum sample result available after booster vaccination, were negative for hepatitis B virus and hepatitis C virus at baseline, and did not have a positive nasal swab PCR or anti-NP antibodies on or before the booster dose. A single booster dose of NUVAXOVID (Original, Wuhan strain) administered 6 months after the second dose of the primary series vaccination elicited robust neutralizing antibody (MN50) responses against the SARS-CoV-2 wild-type virus (ancestral Wuhan strain) at 35 days after booster administration with a neutralizing antibody GMT of 3,812.6 that was higher than that reported at 14 days after completion of primary series vaccination with NUVAXOVID (Original, Wuhan strain) (1,402.3). The ratio of neutralizing antibody titers (MN50) against SARS-CoV-2 wild-type virus (ancestral Wuhan strain) at 35 days post-booster dose versus at 14 days post-primary series vaccination was 2.7 (95% CI: 2.4 – 3.0).

Immunogenicity of a Heterologous Booster dose

Effectiveness of NUVAXOVID (Original, Wuhan strain) booster dose in individuals who completed primary vaccination with another Canadian authorized or approved COVID-19 vaccine is inferred from immunogenicity data reported from an independent study conducted in the United Kingdom (ISRCTN 73765130; EudraCT 2021-002175-19). This multicenter, randomized, controlled Phase 2 trial investigated the immunogenicity of a single booster dose of NUVAXOVID (Original, Wuhan strain) administered at least 70 days after completion of a ChAdOx1 nCov-19 (Oxford-AstraZeneca) primary vaccination series or at least 84 days after completion of a BNT162b2 (Pfizer-BioNTech) primary vaccination series. Participants included adults aged 30 years and older with no history of laboratory-confirmed SARS-CoV-2 infection. In the study, 115 participants received a two-dose primary series of ChAdOx1 nCov-19 and 114 participants received a two-dose primary series of BNT162b2, prior to receiving a single booster dose of NUVAXOVID (Original, Wuhan strain). Neutralizing antibody titers measured by a microneutralization assay were assessed prior to the booster dose and 28 days post-booster dose. A booster response to the NUVAXOVID (Original, Wuhan strain) vaccine was demonstrated regardless of the vaccine used for primary vaccination.

Immunogenicity in Adolescents 12 through 17 years of age

Study 2019nCoV-301

At the cut-off date of 07 September 2022 the immunogenicity analysis population (referred to as the Per-Protocol Immunogenicity [PP-IMM] analysis set) included 220 participants who completed both doses of their primary series vaccination with NUVAXOVID (Original, Wuhan strain), received a single booster dose, completed Day 35 blood samples, did not have a positive nasal swab PCR or positive serum anti-nucleoprotein (NP) antibodies on or before the booster dose (if available), had not received an EUA vaccine and remained blinded to their original treatment assignment during the primary series of vaccination. Of these participants, 110 received a single booster dose of NUVAXOVID (Original, Wuhan strain) after receiving placebo during the initial (pre-crossover) vaccination period followed by active vaccination during the blinded crossover period [Cohort 1] and 110 who received a booster dose after first receiving active vaccination during the initial (pre-crossover) vaccination period followed by placebo during the blinded crossover period [Cohort 2].

Only participants in Cohort 2 were included in the immunogenicity analysis. Immune responses were measured by a validated microneutralization assay against SARS-CoV-2 wild-type virus (ancestral Wuhan strain) that defined the titer as the concentration that yielded >50% viral inhibition [MN_{50}].

In Cohort 2, a single booster dose of NUVAXOVID (Original, Wuhan strain) elicited robust MN_{50} response, 27.7-fold increase in neutralizing antibodies was shown from a GMT of 426.7 pre-booster to a GMT of 11,824.4 post-booster and an approximate 2.7-fold increase from a peak GMT (14 days post-Dose 2) of 4,434.0. The ratio of MN_{50} titers at 28 days post-booster dose versus at 14 days post-primary series vaccination was 2.7 (95% CI: 2.0 – 3.5) (N = 53).

Based on neutralizing antibody responses, non-inferiority was achieved for GMFRs and for the differences in SCRs using the baseline of the first dose of NUVAXOVID (Original, Wuhan strain) in the pre crossover period (Cohort 2) (lower limit of the 95% CI > -10%). Numerically higher immune responses for pseudo-virus-based neutralizing antibody against the Omicron BA.4/5 variant and serum IgG antibody against the Omicron BA.1 variant were also seen after the single booster dose of NUVAXOVID (Original, Wuhan strain). The clinical significance of these higher neutralizing antibodies is unknown.

15 MICROBIOLOGY

No microbiological information is required for this vaccine product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: In a repeat-dose toxicity study conducted in New Zealand White rabbits, 50 mcg SARS-CoV-2 rS with or without 50 mcg Matrix-M adjuvant was administered intramuscularly up to 4 times (days 1, 8, 15 and 36) and demonstrated SARS-CoV-2 rS with Matrix-M adjuvant was well-tolerated with no adverse findings. Effects on clinical pathology parameters (fibrinogen, CRP, and/or globulin), which resolved during the recovery interval, and histopathology (subacute inflammation at injection sites and adjacent tissue), which were decreased at the recovery interval, were consistent with immune stimulation following administration of a vaccine.

Carcinogenicity: NUVAXOVID (Original, Wuhan strain) has not been evaluated for carcinogenicity in animals, as carcinogenicity studies were not considered relevant to this vaccine.

Genotoxicity: In vitro genotoxicity studies were conducted with the Matrix-M adjuvant. The adjuvant was shown to be non-mutagenic in both the bacterial reverse mutation assay and mammalian cell micronucleus assay.

Reproductive and Developmental Toxicology: A developmental and reproductive toxicity study was performed in female rats administered four intramuscular doses (two prior to mating; two during gestation) of 5 micrograms SARS-CoV-2 rS protein (approximately 200-fold excess relative to the human dose of 5 micrograms on a weight- adjusted basis) with 10 micrograms Matrix-M adjuvant (approximately 40-fold excess relative to the human dose of 50 micrograms on a weight-adjusted basis). No vaccine-related adverse effects on fertility, pregnancy/lactation, or development of the embryo/foetus and offspring through post-natal Day 21 were observed.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

NUVAXOVID XBB.1.5

COVID-19 Vaccine, Adjuvanted XBB.1.5

Read this carefully before you start taking **NUVAXOVID XBB.1.5**. 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 **NUVAXOVID XBB.1.5**.

What is NUVAXOVID XBB.1.5 used for?

NUVAXOVID XBB.1.5 is a protein-based vaccine used to prevent the coronavirus disease 2019 (COVID-19) caused by the SARS-CoV-2 virus. It can be given to individuals aged 12 years and older.

How does NUVAXOVID XBB.1.5 work?

NUVAXOVID XBB.1.5 causes the immune system (the body's natural defenses) to produce antibodies and specialized white blood cells that work against the virus, to give protection against COVID-19. Protein-based vaccines use a purified recombinant protein to help our bodies protect against the virus. The addition of the Matrix-M adjuvant helps activate the immune system, which enhances the magnitude of the vaccine-specific response to the purified recombinant spike protein, which may contribute to protection against COVID-19.

The vaccine is given by injection with a needle in the upper arm.

As with any vaccine, NUVAXOVID XBB.1.5 may not fully protect all those who receive it. Even after you/your child have received a dose of the vaccine, continue to follow the recommendations of local public health officials to prevent spread of COVID-19.

You/your child cannot get COVID-19 from this vaccine.

What are the ingredients in NUVAXOVID XBB.1.5?

Medicinal ingredients: 5 micrograms of purified SARS-CoV-2 recombinant spike protein as the active substance.

Non-medicinal ingredients:

- Disodium hydrogen phosphate heptahydrate
- Sodium dihydrogen phosphate monohydrate
- Sodium chloride
- Polysorbate 80

- Sodium hydroxide
- Hydrochloric acid
- Water for Injection

The Matrix-M adjuvant contains saponin, cholesterol, phosphatidylcholine, potassium dihydrogen phosphate disodium hydrogen phosphate dihydrate, sodium chloride and potassium chloride. NUVAXOVID XBB.1.5 does not contain mRNA, antibiotics, or preservatives; there is no gelatin added in NUXAVOID XBB.1.5 as a stabilizer.

NUVAXOVID XBB.1.5 comes in the following dosage forms:

Colourless to slightly yellow, clear to mildly opalescent suspension provided in a clear multidose glass vial with a rubber stopper and a blue flip-off top. Each multidose vial contains 5 doses of 0.5 mL.

Do not use NUVAXOVID XBB.1.5 if:

- You/your child are allergic to the active substance or any of the other ingredients of this vaccine (see What are the ingredients in NUVAXOVID XBB.1.5?).
- You/your child have had an allergic reaction to a previous dose of NUVAXOVID XBB.1.5.
- You/your child currently have 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 take NUVAXOVID XBB.1.5. Talk about any health conditions or problems you/your child may have, including if you/your child:

- Have any allergies or previous problems following administration of NUVAXOVID (Original, Wuhan strain) or NUVAXOVID XBB.1.5, such as an allergic reaction or breathing problems
- Have ever fainted following any needle injection
- Have a bleeding problem, bruise easily or use a blood thinning medication
- Have a high fever or severe infection
- Have any serious illness
- Have previously had episodes of myocarditis (inflammation of the heart muscle) and/or pericarditis (inflammation of the lining outside the heart)
- Your/your child's immune system does not work properly (immunodeficiency) or you/your child are taking medicines that weaken the immune system (such as high-dose corticosteroids, immunosuppressants, or cancer medicines)
- Are pregnant, think you/your child may be pregnant or plan to become pregnant

- Are breastfeeding or plan to breastfeed

Tell your 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 NUVAXOVID XBB.1.5 with other vaccines. Tell your/your child's healthcare professional if you/your child have recently received any other vaccine.

How is NUVAXOVID XBB.1.5 given:

- Your doctor, pharmacist or nurse will inject the vaccine into a muscle (intramuscular injection) in your upper arm
- During and after the injection of the vaccine, your doctor, pharmacist, or nurse will watch over you for around 15 minutes to monitor for signs of an allergic reaction.

Usual dose:

Individuals 12 years of age and older who have been vaccinated with a previously or currently marketed Canadian COVID-19 vaccine series.

NUVAXOVID XBB.1.5 will be given to you/your child as a single dose (0.5 mL injection). You/your child should receive a dose of NUVAXOVID XBB.1.5 at least 6 months after the most recent dose of a Canadian marketed COVID-19 vaccine. No dose adjustment is required based on age.

Individuals 12 years of age and older who have not been vaccinated with a previously or currently marketed Canadian COVID-19 vaccine series.

NUVAXOVID XBB.1.5 will be given to you/your child as two 0.5 mL injections. Each injection will be given on a separate visit 3 weeks apart. It is very important that you return for the second injection, or the vaccine may not work as well.

You/your child should complete the vaccination course with NUVAXOVID XBB.1.5.

Overdose:

If you think you, or a person you are caring for, have received too much NUVAXOVID XBB.1.5, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

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

What are possible side effects from using NUVAXOVID XBB.1.5?

Like all vaccines, NUVAXOVID XBB.1.5 can cause side effects.

The following are common or very common side effects of NUVAXOVID. Most of these side effects are mild and do not last long. Tell your/your child's doctor if you have side effects that bother you:

- headache
- feeling sick (nausea) or getting sick (vomiting)
- muscle ache
- joint pain
- tenderness or pain where the injection is given
- feeling very tired (fatigue)
- generally feeling unwell (malaise)
- redness where the injection is given
- swelling where the injection is given
- fever (> 38°C)
- pain or discomfort in the arm, hand, leg and/or foot (pain in the extremity)

Non-severe and severe allergic reactions, hypoaesthesia (decreased sense of touch or sensation, numbness), paraesthesia (tingling, itching or pricking sensation), and tinnitus (ringing in ears) have also been reported. Myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) have been reported following NUVAXOVID (Original, Wuhan strain) administration.

These are not all the possible side effects you/your child may have when taking NUVAXOVID XBB.1.5. If you/your child experience any side effects not listed here, tell your/your child's healthcare professional.

Should you/your child develop any serious symptoms or symptoms that could be an allergic reaction, seek medical attention immediately. Symptoms of an allergic reaction include:

- feeling faint or light-headed
- changes in your/your child's heartbeat
- shortness of breath
- wheezing
- swelling of your/your child's lips, face, or throat
- hives or rash
- nausea or vomiting
- stomach pain

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

If you/your child have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your/your child's daily activities, tell your/your child's healthcare professional.

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 Novavax, Inc. 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 (http://www.phac-aspc.gc.ca/im/aefi-essi-form-eng.php) and send it to your local Health Unit.

Storage:

Do not use this vaccine after the expiry date, which is stated on the label after EXP. The expiry date refers to the last day of that month.

Your/your child's healthcare professional is responsible storing, supplying and administering this vaccine, as well as disposing of any unused product correctly.

Keep out of reach and sight of children.

If you want more information about NUVAXOVID XBB.1.5:

- 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 http://www.NovavaxCovidVaccine.com, or by calling 1-855-239-9172.

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