▼ This vaccine is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – NUVAXOVID (SARS-COV-2 RS [NVX-COV2373]) SUSPENSION FOR INJECTION

1 NAME OF THE MEDICINE

SARS-CoV-2 rS (NVX-CoV2373)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

These are multidose vials which contain 5 doses or 10 doses of 0.5 mL per vial (see section 6.5 Nature and contents of container). One dose (0.5 mL) contains 5 micrograms of SARS-CoV-2 spike protein* and is adjuvanted with Matrix-M.

Adjuvant Matrix-M contains, per 0.5 mL dose: *Quillaja saponaria* saponins fraction A (42.5 micrograms) and *Quillaja saponaria* saponins fraction C (7.5 micrograms), see section 6.5 Nature and Contents of Container.

*produced by recombinant DNA technology using a baculovirus expressions system in an insect cell line that is derived from Sf9 cells of the *Spodoptera frugiperda* species.

For the full list of excipients, see section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

Suspension for injection.

NUVAXOVID is colourless to slightly yellow, clear to mildly opalescent.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 in individuals 12 years of age and older.

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

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

Primary series

NUVAXOVID is administered intramuscularly as a course of 2 doses of 0.5 mL each. It is recommended that the second dose is to be administered 3 weeks after the first dose, see section 5.1 Pharmacodynamic Properties.

Additional Dose

An additional dose of NUVAXOVID (0.5 mL) may be administered intramuscularly approximately 6 months after completion of a primary series in individuals 18 years of age and older.

The decision when and for whom to implement an additional dose of NUVAXOVID should be made based on available vaccine safety and effectiveness data (see sections 4.8 Adverse Effects and 5.1 Pharmacodynamic Properties), in accordance with official recommendations.

The use of this vaccine should be in accordance with clinical recommendations in Australia, made by ATAGI in the Australian Immunisation Handbook.

For precautions for administering the vaccine, see section 4.4 Special Warnings and Precautions for Use.

Method of administration

NUVAXOVID is for intramuscular injection only, preferably into the deltoid muscle of the upper arm.

Do not inject the vaccine intravascularly, subcutaneously, or intradermally.

This vaccine should be handled by a healthcare professional using aseptic techniques to ensure the sterility of each dose. The vaccine contains no antimicrobial preservative.

The vaccine comes ready to use. Do not dilute.

Inspect the vial:

- Gently swirl the multidose vial before and in between each dose withdrawal. Do not shake.
  - Each multidose vial contains a colourless to slightly yellow, clear to mildly opalescent suspension free from visible particles.
  - Visually inspect the contents of the vial for visible particulate matter and/or discolouration prior to administration. Do not administer the vaccine if either are present.

Administer the vaccine:

- An overfill is included per vial to ensure that a maximum of five doses (vial of 2.5 mL) or ten doses (vial of 5 mL) of 0.5 mL each can be extracted.
- 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.
- Use a separate sterile needle and syringe for each individual dose, prior to use in a vaccination session.
  - Do not mix the vaccine in the same syringe with any other vaccines or medicinal products.
  - Do not pool excess vaccine from multiple vials.

Storage after first needle puncture:

- NUVAXOVID contains no antimicrobial preservative. Store the opened vial between 2°C to 25°C for up to 12 hours after first puncture, see section 6.3 Shelf life.
- Record the date and time of discard on the vial label.

Discard:

- Discard this vaccine if not used within 12 hours after first puncture of the vial, see section 6.3 Shelf life.

For instructions regarding disposal of the vaccine, see section 6.6 Special Precautions for Disposal.

4.3 CONTRAINDICATIONS

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypersensitivity and anaphylaxis

Events of anaphylaxis have been reported with COVID-19 vaccines including NUVAXOVID. 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. A second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose of NUVAXOVID.

Myocarditis and Pericarditis

There is an increased risk of myocarditis and pericarditis in males and females following vaccination with NUVAXOVID (see section 4.8 Adverse Effects (Undesirable effects)). These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days.

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

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinated individuals, parents and 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. Non-specific symptoms of myocarditis and pericarditis also include fatigue, nausea and vomiting, abdominal pain, dizziness or syncope, oedema and cough. Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

For further details, please refer to the relevant clinical guidelines developed by the Australian Technical Advisory Group on Immunisation.

Anxiety-related reactions

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation, or stress-related reactions may occur in association with vaccination as a psychogenic response to the needle injection. It is important that precautions are in place to avoid injury from fainting.

Concurrent illness

Vaccination should be postponed in individuals suffering from an acute severe febrile illness or acute infection. The presence of a minor infection and/or low-grade fever should not delay vaccination.

Thrombocytopenia and coagulation disorders

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

Immunocompromised individuals

The efficacy, safety, and immunogenicity of the vaccine has been assessed in a limited number of immunocompromised individuals. The efficacy of NUVAXOVID may be lower in immunosuppressed individuals.

Duration of protection

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

Limitations of vaccine effectiveness

Individuals may not be fully protected until 7 days after their second dose. As with all vaccines, vaccination with NUVAXOVID may not protect all vaccine recipients.

Traceability

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

Use in the elderly

No dosage adjustment is required in individuals ≥ 65 years of age.

Paediatric use

The safety and efficacy of NUVAXOVID in children less than 12 years of age have not yet been established. Limited data are available.

Effects on laboratory tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

Co-administration of NUVAXOVID with inactivated influenza vaccines has been evaluated in a limited number of adult participants in an exploratory clinical trial sub-study (2019nCoV-302).

The binding antibody response to SARS-CoV-2 was lower when NUVAXOVID was given concomitantly with inactivated influenza vaccine. The seroconversion rates of these participants, given NUVAXOVID and flu vaccine concomitantly, were similar to the seroconversion rates of the participants in the main study who received NUVAXOVID alone. The clinical significance of this is unknown, see section 4.8 Adverse Effects and section 5.1 Pharmacodynamic Properties. Concomitant administration of NUVAXOVID with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation

Effects on fertility

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

A developmental and reproductive toxicity study was performed in female rats administered four intramuscular doses (2 prior to mating; 2 during gestation) of 5 micrograms SARS-CoV-2 rS protein (approximately 200-fold excess relative to the human dose of 5 micrograms on a body surface-adjusted basis) with 10 micrograms Matrix-M adjuvant (approximately 7-fold excess relative to the human dose of 50 micrograms on a body surface-adjusted basis). No vaccine-related adverse effects on female fertility, pregnancy/lactation, or development of the embryo/fetus and offspring through post-natal Day 21 were observed. The study did not evaluate effects on male fertility.

Use in pregnancy – Pregnancy Category B1

There is limited experience with use of NUVAXOVID in pregnant women.

A combined fertility and developmental toxicity study in rats did not show vaccine related adverse effects on embryofetal development (see Effects on fertility).

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

Use in lactation.

It is unknown whether NUVAXOVID is excreted in human milk.

4.7 Effects on ability to drive and use machines

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

4.8 Adverse effects (Undesirable effects)

Summary of safety profile

Participants 18 years of age and older – after 2-dose primary series

The safety of NUVAXOVID was evaluated from an interim analysis of pooled data from 5 ongoing and completed clinical trials conducted in Australia, South Africa, the United Kingdom (UK), the United States (US) and Mexico. At the time of the analysis, a total of 49,948 participants aged 18 years and older received at least 1 dose of NUVAXOVID (n=30,077) or placebo (n=19,871). At the time of vaccination, the median age was 48 years (range 18 to 95 years). The median duration of follow-up was 70 days post-Dose 2, with 32,993 (66%) participants completing more than 2 months follow-up post-Dose 2.

Of the pooled reactogenicity data, which includes participants aged 18 and older enrolled in the 5 ongoing and completed clinical trials who received NUVAXOVID (n=30,077) or placebo (n=19,871), the most frequent adverse reactions following Dose 1 were injection site pain/tenderness (55%), fatigue/malaise (28%), headache (24%), myalgia (22%), arthralgia (8%) and nausea or vomiting (6%). The most frequent adverse reactions following Dose 2 were injection site pain/tenderness (74%), fatigue/malaise (50%), myalgia (44%), headache (41%), arthralgia (20%), and nausea or vomiting

(11%), erythema (6%), swelling (6%) and pyrexia (5%). Adverse reactions were usually mild to moderate in severity with a median duration of less than or equal to 2 days for local events and less than or equal to 1 day for systemic events following vaccination.

Overall, there was a higher incidence of adverse reactions in younger age groups: the incidence of injection site pain/tenderness, fatigue/malaise, myalgia, headache, arthralgia, and nausea or vomiting was higher in adults aged 18 to less than 65 years than those aged 65 years and above for Dose 1 and Dose 2.

Local and systemic adverse reactions were more frequently reported after Dose 2 than Dose 1.

Licensed inactivated seasonal influenza vaccines were co-administered on the same day as the Dose 1 of NUVAXOVID (n=217) or placebo (n=212) in the opposite deltoid muscle of the arm in 429 participants enrolled in an exploratory Phase 3 (2019nCoV-302) sub-study. The frequency of local and systemic adverse reactions in the influenza sub-study population was higher than in the main study population following Dose 1 in both NUVAXOVID and placebo recipients. Frequences of solicted local and systemic adverse reactions were similar between the sub-study and main study populations following Dose 2 of NUVAXOVID alone.

Overall, a lower frequency of reactogenicity events was associated with greater age across the 5 main studies and seasonal influenza vaccine sub-study.

Adolescents 12 to 17 years of age – after 2-dose primary series

The safety of NUVAXOVID in adolescents was evaluated in an interim analysis of the paediatric expansion portion of an ongoing Phase 3 multicentre, randomised, observer-blinded, placebo-controlled study (Study 2019nCoV-301).

Safety data were collected in 2,232 participants 12 to 17 years of age, with and without evidence of prior SARS CoV-2 infection, in the US who received at least 1 dose of NUVAXOVID (n=1,487) or placebo (n=745).

Demographic characteristics were similar among participants who received NUVAXOVID and those who received placebo.

The most frequent adverse reactions after Dose 1 were injection site pain/tenderness (65%), myalgia (34%), headache (30%), fatigue/malaise (29%), nausea or vomiting (8%), and arthralgia (7%). The most frequent adverse reactions after Dose 2 were injection site pain/tenderness (75%), fatigue/malaise (58%), headache (57%), myalgia (49%), nausea or vomiting (20%), pyrexia (17%), arthralgia (16%), swelling (8%) and erythema (8%). Fever was observed more frequently in adolescents 12 to 17 years of age compared with adults, with the frequency being very common after the second dose in adolescents. Adverse reactions were usually mild to moderate in severity with a median duration of less than or equal to 2 days for local events and less than or equal to 1 day

for systemic events following vaccination.

Tabulated list of adverse reactions

Adverse reactions observed in individuals 12 years of age and older during clinical studies are listed below according to the following frequency categories:

Very common (≥ 1/10),
Common (≥ 1/100 to < 1/10),

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

Table 1: Adverse reactions from clinical trials in individuals 12 years of age and older

MedDRA System Organ Class	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to <1/100)	Rare (≥ 1/10,000 to <1/1,000)	Very rare (≥ 1/10,000)	Not known (cannot be estimated from the available data)
Blood and lymphatic system disorders			Lymphadenopathy			
Nervous system disorders	Headache					
Vascular disorders			Hypertension[d]			
Gastrointestinal disorders	Nausea or vomiting[a]					
Skin and subcutaneous tissue disorders			Rash Erythema Pruritus Urticaria			
Musculoskeletal and connective tissue disorders	Myalgia[a], Arthralgia[a]					
General disorders and administration site conditions	Injection site tenderness[a], Injection site pain[a], Fatigue[a], Malaise[a, b]	Injection site redness[a,c], Injection site swelling[a], Pyrexia[a, e], Chills, Pain in extremity	Injection site pruritus			

[a] Higher frequencies of these events were observed after the second dose.
[b] This term also included events reported as influenza-like illness.
[c] This term includes both injection site redness and injection site erythema (common).
[d] Hypertension was not reported in adolescents 12 to 17 years in the clinical study
[e] Pyrexia was observed more frequently in adolescents 12 to 17 years compared with adults, with the frequency being very common after the second dose in adolescents.

Participants 18 years of age and older – after booster dose

The safety and immunogenicity of a booster dose of NUVAXOVID was evaluated in an ongoing Phase 2 randomised, placebo-controlled, observer-blinded clinical study (Study 2019nCoV-101, Part 2) conducted in participants aged 18 to 84 years of age. A total of 258 participants received 2 doses of NUVAXOVID (0.5 mL, 3 weeks apart) as the primary vaccination series. A subset of 105 participants (Safety Analysis Set) were randomised and received a booster dose of NUVAXOVID approximately 6 months after receiving Dose 2 of the primary series. The most frequent solicited adverse reactions were injection site tenderness (81%), fatigue (63%), injection site pain (55%), muscle pain (51%),

malaise (47%), headache (46%), joint pain (29%), and fever (17%) with a median duration of 1 to 3 days following vaccination.

In a second ongoing Phase 2a/b randomised, placebo-controlled, observer-blinded clinical study conducted in South Africa (Study 2019nCoV-501), the immunogenicity and safety of a booster dose of NUVAXOVID was evaluated in healthy human immunodeficiency virus (HIV)-negative participants 18 to 84 years of age (Cohort 1) and medically stable people living with HIV (PLWH) 18 to 64 years of age (Cohort 2). Overall, 1,898 participants (Safety Analysis Set) received a booster dose of NUVAXOVID approximately 6 months after receiving the second dose of a 2-dose primary series. Solicited adverse reactions were not collected following the booster dose. The unsolicited adverse reaction profile for the booster dose was similar to that of the primary series presented in Table 1.

Booster dose following primary vaccination with other COVID-19 vaccine

The safety of NUVAXOVID as a heterologous booster in individuals whose primary vaccination series was with other COVID-19 vaccines has been reported in the COV-BOOST study conducted in the UK (ISRCTN 73765130). This was an independent, randomised, controlled, Phase 2 trial that evaluated a single heterologous booster vaccination against COVID-19 in adults aged 30 years and older, with no history of laboratory-confirmed SARS-CoV-2 infection, at least 10 weeks after a primary vaccination series. Within the group assigned to receive a full dose of NUVAXOVID (0.5 mL) were 115 participants who previously received 2 doses of VAXZEVRIA (median age 65 years) and 114 who had received 2 doses of COMIRNATY (mean age 63 years). The booster dose of NUVAXOVID was given a median of 76 days after the VAXZEVRIA primary series and 105 days after the COMNIRNATY primary series. Additionally, another 220 participants received a half dose of NUVAXOVID (0.25 mL). Review of the adverse reactions over the 28 days following receipt of the NUVAXOVID booster did not identify any new safety concerns, as compared with adverse reactions reported following 2 doses of NUVAXOVID given as a primary series. The safety data are limited by the small sample size of the study.

Description of selected adverse reactions

Throughout the clinical trials, an increased incidence of hypertension following vaccination with NUVAXOVID (n=46, 1.0%) as compared with placebo (n=22, 0.6%) was observed in older adults during the 3 days following vaccination.

Post-marketing experience

The following adverse reactions have been spontaneously reported during post-authorisation use of NUVAXOVID. As these reactions were derived from spontaneous reports, the frequencies could not be determined and are thus considered as not known.

Table 2: Adverse reactions from post-marketing experience

System Organ Class	Adverse Drug Reaction
Immune system disorders	Anaphylaxis
Cardiac disorders	Pericarditis, myocarditis
Nervous system disorders	Hypoaesthesia, paraesthesia
Ear and labyrinth disorders	Tinnitus

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

No case of overdose has been reported. In the event of an overdose, the individual should be monitored and provided with symptomatic treatment as appropriate.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Other viral vaccines, ATC code: J07BX03

Mechanism of action

NUVAXOVID is composed of purified full-length SARS-CoV-2 recombinant spike (S) protein that is stabilised 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 2 vaccine components elicit B- and T-cell immune responses to the S protein, including neutralising antibodies, which protect against COVID-19.

Clinical trials

Two early phase clinical trials were conducted as clinical Study 2019nCoV-101; a Phase 1 (first-in-human)/Phase 2, randomized, observer-blinded, placebo-controlled trial evaluating the safety and immunogenicity of 5-µg and 25-µg doses of SARS-CoV-2 rS with or without 50 µg Matrix-M adjuvant. The Phase 1 study in 131 healthy adult participants aged 18- 59 was conducted in Australia (Part 1), and the Phase 2 study in 1,283 healthy adult participants aged 18- 84 was conducted in both Australia and the US (Part 2).

Part 1: Two-dose regimens of 5 µg or 25 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant, administered 21 to 28 days apart as a bedside mixture, induced robust immune responses (anti-S protein IgG, wild-type neutralising, and hACE2 receptor binding inhibition), peaking 2 weeks after second vaccination (Day 35). Matrix-M adjuvant was antigen sparing, induced high levels of

functional antibodies, and showed a Th1-biased immune response. No difference in dose response was seen between the 5-µg and 25-µg doses.

Part 2: Two-dose regimens of 5 µg or 25 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant, administered 21 days apart as co-formulated drug product (NUVAXOVID), showed similar results (to Part 1), at Day 35.

Both dose levels were well tolerated and induced robust immune responses after the second vaccination (Day 35). Collectively, the data from Part 1 and Part 2 of Clinical Study 2019nCoV-101 supported selection and further development of the 2-dose 5 µg adjuvanted vaccine. The clinical efficacy, safety, and immunogenicity of NUVAXOVID is being evaluated in 2 pivotal, placebo-controlled, Phase 3 studies: Study 1 (2019nCoV-301) conducted in North America and Study 2 (2019nCoV-302) conducted in the UK, and a Phase 2a/b study, Study 3, conducted in South Africa.

Study 1 (2019nCoV-301) - 2-dose Primary Series

Study 1 is an ongoing Phase 3, multicentre, randomised, observer-blinded, placebo-controlled study conducted in participants 18 years of age and older in the US and Mexico (main study) expanded to include a paediatric cohort including participants 12 to < 18 years of age in the US (paediatric expansion).

Participants 18 years of age and older

Upon enrolment in the main study, participants were stratified by age (18 to 64 years and ≥ 65 years) and assigned in a 2:1 ratio to receive NUVAXOVID 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 breastfeeding; or had a history of laboratory-confirmed diagnosed COVID-19. Participants with clinically stable underlying comorbidity were included as were participants with well-controlled HIV infection.

Enrolment of adults was completed in February 2021. Participants will be followed for up to 24 months after the first dose for assessments of safety, and efficacy against COVID-19. Following collection of sufficient safety data to support an application for provisional approval, initial recipients of placebo were invited to receive 2 injections of NUVAXOVID 21 days apart and initial recipients of NUVAXOVID to receive 2 injections of placebo 21 days apart ('blinded crossover'). All participants were offered the opportunity to continue to be followed in the study.

The primary efficacy analysis population (referred to as the Per-Protocol Efficacy [PP-EFF] analysis set) included 25,657 participants who received either NUVAXOVID (n=17,272) or placebo (n=8,385), received 2 doses (Dose 1 on Day 0; Dose 2 at Day 21,), did not experience an exclusionary protocol deviation, and did not have evidence of SARS-CoV-2 infection through 7 days after the second dose.

Demographic and baseline characteristics were balanced amongst participants who received NUVAXOVID and those who received placebo. In the PP-EFF analysis set for participants who received NUVAXOVID, the median age range was 47 years (range: 18 to 95 years); 88% (n=15,228) were 18 to 64 years old and 12% (n=2,044) were aged 65 and older; 48% were female; 94% were from the US 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 1 pre-existing comorbidity or lifestyle characteristic associated with an increased risk of severe COVID-19 was present in 16,455 (95%) participants. Comorbidities included: obesity (body mass index (BMI) ≥ 30 kg/m^2); chronic lung disease; diabetes mellitus type 2; cardiovascular disease; or chronic kidney disease. 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.

COVID-19 cases were confirmed by polymerase chain reaction (PCR) testing through a central laboratory. Vaccine efficacy is presented in Table 3.

Table 3: Vaccine efficacy analyses of PCR-confirmed COVID-19 with onset from 7 days after second vaccination[1] - PP-EFF analysis set; Study 1 (2019nCoV-301)

Subgroup	NUVAXOVID			Placebo			% Vaccine Efficacy (95% CI)
	Partici-pants N	COVID-19 cases n (%)	Incidence Rate Per Year Per 1,000 People[2]	Partici-pants N	COVID-19 cases n (%)	Incidence Rate Per Year Per 1,000 People[2]	
Primary efficacy endpoint							
All participants	17,272	17 (0.098)	5.59	8,385	79 (0.942)	58.30	90.41% (83.81, 94.32) [3,4]

1 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 up to 6 days after the second dose, and who had received the full prescribed regimen of trial vaccine.

2 Mean disease incidence rate per year in 1,000 people.

3 Modified Poisson regression with logarithmic link function, treatment group and age strata as fixed effects and robust error variance [Zou 2004]. Mean incidence was calculated with weighting for 18 to < 65-year and ≥ 65-year groups reflective of the distribution seen in the study population (i.e., observed margins [OM] option for LSMEANS statement in SAS PROC GENMOD).

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

Vaccine efficacy of NUVAXOVID to prevent the onset of COVID-19 from 7 days after Dose 2 was 90.41% (83.81, 94.32). No cases of moderate or severe COVID-19 were reported in the 17,272 NUVAXOVID participants compared with 4 of severe COVID-19 reported in the 8,385 placebo recipients in the PP-EFF analysis set.

Subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates for male and female participants and racial groups, and across participants with medical comorbidities associated with high risk of severe COVID-19. There were no meaningful clinical differences in overall vaccine efficacy in participants who were at increased risk of severe COVID-19 including those with 1 or more comorbidities that increase the risk of severe COVID-19 (eg, BMI ≥ 30 kg/m^2, chronic lung disease, diabetes mellitus type 2, cardiovascular disease, and chronic kidney disease).

Efficacy results reflect enrolment that occurred during the time period when strains classified as Variants of Concern or Variants Being Monitored were predominantly circulating in the 2 countries (US and Mexico) where the study was conducted. Sequencing data were available for 61 of the 77 endpoint cases (79%). Of these, 48 out of 61 (79%) were identified as Variants of Concern or Variants of Interest. The most common Variants of Concern were Alpha with 31/61 cases (51%), Beta (2/61, 4%) and Gamma (2/61, 4%), while the most common Variants of Interest were Iota with 8/61 cases (13%) and Epsilon 3/61 (5%).

Efficacy in Adolescents 12 to 17 years of age

The assessment of efficacy and immunogenicity of NUVAXOVID in adolescent participants 12 to 17 years of age occurred in the US in the ongoing paediatric expansion portion of the Phase 3 2019nCoV-301 study.

A total of 1,787 participants assigned in a 2:1 ratio to receive 2 doses of NUVAXOVID (n=1,197) or placebo (n=590) by intramuscular injection 21 days apart represented the primary efficacy population.

COVID-19 was defined as first episode of PCR-confirmed mild, moderate, or severe COVID-19 with at least 1 or more of the predefined symptoms within each severity category. There were 20 cases of PCR-confirmed symptomatic mild COVID-19 (NUVAXOVID, n=6; placebo, n=14) resulting in a point estimate of efficacy of 79.56% (95% CI: 46.87, 92.13).

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 where sequence data are available (11/20, 55%).

Immunogenicity in Adolescents 12 to 17 years of age

An analysis of the SARS-CoV-2 neutralising antibody response 14 days after Dose 2 (Day 35) was conducted in adolescent participants seronegative to anti-SARS-CoV-2 nucleoprotein (NP)/PCR-negative at baseline compared with that observed in seronegative/PCR-negative adult participants aged 18 to less than 26 years from the main study, in adults (Per Protocol Immunogenicity (PPIMM) Population, before crossover). Noninferiority (lower bound 95% CI for the geometric mean ratio [GMR] >0.67 [1.3]) was met as presented in Table 4.

Table 4: Adjusted Ratio of Geometric Mean of Microneutralisation Assay Neutralising Antibody Titers for SARS-CoV-2 S Wild-Type Virus at 14 Days After Dose 2 and Presented by Age Group (PPIMM Analysis Set)[1]

Assay	Timepoint	Paediatric Expansion (12 to < 18 Years) N=393	Adult Main Study (18 to < 26 Years) N=415	12 to < 18 Years versus 18 to < 26 Years
		GMT 95% CI[2]	GMT 95% CI[2]	GMR 95% CI[2]
Microneutralisation (1/dilution)	Day 35 (14 days after Dose 2)	3834.0 (3402.7, 4320.0)	2633.6 2611.8 (2367.4, 2881.5)	1.46 1.5 (1.3, 1.7) [3]

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; GMR = ratio of GMT, which is defined as the ratio of 2 GMTs for comparison of 2 age cohorts; GMT = geometric mean titer; LLOQ = lower limit of quantitation; N = number of participants in assay-specific PP-IMM Analysis Set in each part of study with non-missing response at each visit; PP-IMM = Per-Protocol Immunogenicity; SARS-CoV-2 = severe acute respiratory syndrome coronavirus2.

[1] Table includes participants in the active vaccine group only.

[2] An ANCOVA with age cohort as main effect and baseline MN Assay neutralising antibodies as covariate was performed to estimate the GMR. Individual response values recorded as below the LLOQ were set to half LLOQ.

[3] Represents (n1, n2) populations defined as:

n1 = number of participants in adult main study (18 to < 26 years) with non-missing neutralising antibodies result

n2 = number of participants in paediatric expansion (12 to <18 years) with non-missing neutralising antibodies result

Study 2 (2019nCoV-302) - 2-dose Primary Series

Study 2 is aPhase 3, multicenter, randomised, observer-blinded, placebo-controlled study in participants 18 to 84 years of age in the UK. Upon enrolment, participants were stratified by age (18 to 64 years; 65 to 84 years) to receive NUVAXOVID 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. Participants with known stable infection with HIV, hepatitis C virus (HCV), or hepatitis B virus (HBV) were not excluded from enrolment.

Enrolment was completed in November 2020. Participants were followed for up to 12 months after the primary vaccination series for assessments of safety, and efficacy against COVID-19.

The primary efficacy PP-EFF analysis set for the pre-specified complete analysis of the primary efficacy endpoint included 14,039 participants who received either NUVAXOVID (n= 7,020) or placebo (n= 7,019), received 2 doses (Dose 1 on day 0; Dose 2 at median 21 days (IQR 21-23), range 16-45, did not experience an exclusionary protocol deviation, and did not have evidence of SARS-CoV-2 infection through 7 days after the second dose.

Demographic and baseline characteristics were balanced amongst participants who received NUVAXOVID and participants who received placebo. In the PP-EFF analysis set for participants who received NUVAXOVID, the median age was 56.0 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; 94% were White; 3% were Asian; 1% were multiple races, <1% were Black or African American; and <1% were Hispanic or Latino; and 45% had at least 1 comorbid condition.

Table 5: Vaccine efficacy analysis of PCR-confirmed COVID-19 with onset at least 7 days after the second vaccination - (PP-EFF population): Study 2 (2019nCoV-302)

Subgroup	NUVAXOVID			Placebo			% Vaccine Efficacy (95% CI)
	Partici-pants N	COVID-19 cases n (%)	Incidence Rate Per Year Per 1,000 People[1]	Partici-pants N	COVID-19 cases n (%)	Incidence Rate Per Year Per 1,000 People[1]	
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)[2,3]
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[2] (79.7, 94.9)

Subgroup	NUVAXOVID			Placebo			% Vaccine Efficacy (95% CI)
	Partici-pants N	COVID-19 cases n (%)	Incidence Rate Per Year Per 1,000 People[1]	Partici-pants N	COVID-19 cases n (%)	Incidence Rate Per Year Per 1,000 People[1]	
65 to 84 years of age	1,953	1 (0.10)[3]	---	1,957	9 (0.9)[2]	---	88.9%[4] (20.2, 99.7)

1 Mean disease incidence rate per year in 1000 people.

2 Based on log-linear model of PCR-confirmed COVID-19 infection incidence rate using Poisson regression with treatment group as fixed effects and robust error variance, where VE = 100 × (1 – relative risk)

3 Met primary efficacy endpoint criterion for success with a lower bound confidence interval (LBCI) > 30%, efficacy has been confirmed at the interim analysis.

4 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.

These results reflect enrolment that occurred during the time period when the B.1.17 (Alpha) variant was circulating in the UK. Identification of the Alpha variant was based on S gene target failure by PCR. Data were available for 95 of the 106 endpoint cases (90%). Of these, 66 out of 95 (69%) were identified as the Alpha variant with the other cases classified as non-Alpha.

No cases of severe COVID-19 were reported in the 7,020 NUVAXOVID participants compared with 4 cases of severe COVID-19 reported in the 7,019 placebo recipients in the PP-EFF analysis set.

Vaccine efficacy of NUVAXOVID to prevent the onset of COVID-19 from 7 days after Dose 2 was 89.7% (PP-EFF analysis set) for any strain or variant of SARS-CoV-2 and 86.3% (post-hoc analysis of the PP-EFF analysis set) for the B.1.1.7 (Alpha) variant of SARS-CoV-2, which comprised 66 out of 95 (69%) of the endpoint cases that were sequenced.

Licensed seasonal influenza vaccine co-administration sub-study of Study 2 (2019nCoV-302)

Overall, 429 participants were co-vaccinated with inactivated seasonal influenza vaccines; 217 sub-study participants received NUVAXOVID and 212 received placebo. Demographic and baseline characteristics were balanced amongst participants who received NUVAXOVID and participants who received placebo. In the per-protocol immunogenicity (PP-IMM) analysis set for participants who received NUVAXOVID (n = 191), median age was 40.0 years (range: 22 to 70 years); 93% (n = 178) were 18 to 64 years old and 7% (n = 13) were aged 65 to 84, 43% were female; 75% were White; 23% were multiracial or from ethnic minorities; and 27% had at least 1 comorbid condition. Co-administration resulted in no change to influenza vaccine immune responses as measured by hemagglutination inhibition (HAI) assay. A 30% reduction in antibody responses to NUVAXOVID was noted as assessed by an anti-S IgG assay with seroconversion rates similar to participants who did not receive concomitant influenza vaccine (see section 4.5 Interactions with Other Medicines and Forms of Interactions and section 4.8 Adverse Effects).

Study 3 (2019nCoV-501) -2-dose Primary Series

Study 3 is a Phase 2a/b, multicenter, randomised, observer-blinded, placebo-controlled study in HIV-negative participants 18 to 84 years of age and people living with HIV (PLWH) 18 to 64 years of age in South Africa. PLWH were medically stable (free of opportunistic infections), receiving highly active and stable antiretroviral therapy, and having an HIV-1 viral load of < 1000 copies/mL.

The PP-EFF for the pre-specified complete analysis of the primary efficacy endpoint included 2,770 participants who received either NUVAXOVID (n=1,408) or placebo (n=1,362), received 2 doses (Dose 1 on Day 0; Dose 2 on Day 21), did not experience an exclusionary protocol deviation, and did not have evidence of SARS-CoV-2 infections through 7 days after the second dose.

Demographic and baseline characteristics were balanced amongst participants who received NUVAXOVID and participants who received placebo. in the RR-EFF analysis set for participants who received NUVAXOVID, median age was 28 years (range 18 to 84 years); 40% were female; 91% were Black/African American; 2% were White; 3% were multiple races; 1% were Asian; and 2% were Hispanic or Latino; and 5.5% were HIV-positive.

A total of 147 symptomatic mild, moderate, or severe COVID-19 cases among all adult participants, seronegative (to SARS-CoV-2) at baseline, were accrued for the complete analysis (PP-EFF analysis set) of the primary efficacy endpoint, with 51 (4%) cases for NUVAXOVID versus 96 (7%) cases for placebo. The resultant vaccine efficacy of NUVAXOVID was 48.6% (95% CI: 28.4 - 63.1).

These results reflect enrolment that occurred during the time period when the B.1.351 (Beta) variant was circulating in South Africa.

Immunogenicity of NUVAXOVID as a homologous or heterologous booster dose

Immunogenicity in participants 18 years of age and older – after booster dose

Study 2019nCoV-101, Part 2

The safety and immunogenicity of a booster dose of NUVAXOVID was evaluated in an ongoing Phase 2 randomised, observer-blinded, placebo-controlled clinical study administered as a single booster dose (Study 2019nCoV-101, Part 2) in healthy adult participants aged 18 to 84 years of age who were seronegative to SARS-CoV-2 at baseline. A total of 258 participants received 2 doses of NUVAXOVID (0.5 mL, 5 micrograms 3 weeks apart) as the primary vaccination series. A subset of 105 participants received a booster dose of NUVAXOVID approximately 6 months after receiving Dose 2 of the primary series.

A single booster dose of NUVAXOVID induced an approximate 31-fold increase in the immune response against the ancestral (Wuhan) strain 28 days after receipt of the dose (Day 217) with anti-S protein IgG units of 200,243 EU compared with a GMT of 6,151 EU pre-booster (Day 189) and an approximate 4.6-fold increase from that reported at Day 35 (43,905 EU), 14 days following Dose 2 of the primary series.

An approximate 80-fold increase in neutralising antibodies was shown from a GMT of 68 pre-booster (Day 189) to a GMT of 5,542 post-booster (Day 217) and an approximate 6.5-fold increase from that reported at Day 35 (14 days post-Dose 2) a GMT of 855.

For the variants of concern, 2 assays were used to assess immune responses. An assay comparing anti-rS IgG activity (n = 70; 24 for Omicron BA.1) across the same strains demonstrated a 4.6-fold (Ancestral), 5.3-fold (Beta), 7.2-fold (Delta), and 9.8-fold (Omicron BA.1) increase from 2 weeks after the primary series (Day 35) to 28 days post-booster (Day 217). A second assay comparing wild-type neutralisation titers (MN_{99}) (n = 70; 24 for Omicron BA.1) showed a 6.5-fold (Ancestral), 19.0-fold (Beta), 14.0-fold (Delta), and 7.4-fold (Omicron BA.1) increase from 2 weeks after the primary series (Day 35) to 28 days post-booster (Day 217).

Study 2019nCoV-501

In Study 3, a Phase 2a/b randomised, observer-blinded, placebo-controlled study, the safety and immunogenicity of booster dose was evaluated in healthy HIV-negative adult participants 18 to 84 years of age and medically stable PLWH 18 to 64 years of age who were seronegative to SARS-CoV-2 at baseline. A total of 1,173 participants (PP-IMM Analysis Set) received a booster dose of NUVAXOVID approximately 6 months after completion of the primary series of NUVAXOVID (Day 201).

Anti-S protein IgG units at Day 236 increased 17.1-fold from Day 201 (5,950.3 EU/mL) to 114,679.1 EU/mL, which was approximately 2.5 -fold higher than that reported at Day 35 (46,304.7 EU/mL) of the initial vaccination period. At Day 386, anti-S protein IgG decreased to 44,487.6 EU/mL, which was similar to that reported at Day 35 (46,304.7 EU/mL) of the initial vaccination period.

An approximate 20.6-fold increase in neutralising antibodies was shown from a GMT of 146 pre-booster (Day 201) to a GMT of 3,726.3 post-booster (Day 236) which was approximately 3 fold higher than that reported at Day 35 (1,168.4) of the initial vaccination period. At Day 386, neutralizing antibody GMT decreased to 1,998.9, which was approximately 2-fold higher than that reported at Day 35 (1,168.4) of the initial vaccination period.

Immunogenicity of a booster dose following primary vaccination with other COVID-19 vaccines

The effectiveness of NUVAXOVID as a heterologous booster in individuals whose primary vaccination series was with other COVID-19 vaccines, has been reported in the COV-BOOST study conducted in the UK (ISRCTN 73765130). This was an independent randomised, controlled, phase 2 trial that evaluated a heterologous booster vaccination against COVID-19 in adults aged 30 years and older, at least 10 weeks after a primary vaccination series, with no history of laboratory confirmed SARS-CoV-2 infection. Within the group assigned to receive NUVAXOVID were 115 individuals who previously received VAXZEVRIA and 114 who had received COMIRNATY. NUVAXOVID induced significantly higher anti-spike IgG at 28 days post booster compared with the control (a quadrivalent meningococcal vaccine). It is noted that the incremental increase in antibody concentrations was lower following a third (booster) dose with NUVAXOVID than following mRNA vaccines. The geometric mean (GM) fold rise after a single booster dose of NUVAXOVID exceeded the pre-specified GM-fold rise of 1.75 (compared with control) that was considered to be an immunologically important difference.

Elderly population

NUVAXOVID was assessed in participants 18 years of age and older. The efficacy of NUVAXOVID was consistent between elderly (≥ 65 years) and younger individuals (18 to 64 years).

5.2 PHARMACOKINETIC PROPERTIES

Not applicable.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

In vitro genotoxicity studies including bacterial reverse mutation, chromosomal aberrations in Chinese Hamster Ovary (CHO) cells and mammalian micronuclei in CHO cells were conducted with the Matrix-M adjuvant. The adjuvant was shown to be non-genotoxic.

Carcinogenicity

Carcinogenicity studies were not performed. The components of the vaccine are not expected to have carcinogenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

- Dibasic sodium phosphate heptahydrate
- Monobasic sodium phosphate monohydrate
- Sodium chloride
- Polysorbate 80
- Sodium hydroxide (for adjustment of pH)
- Hydrochloric acid (for adjustment of pH)
- Water for Injections
- Adjuvant (Matrix M)
    - *Quillaja saponaria* saponins fraction A
    - *Quillaja saponaria* saponins fraction C
    - Cholesterol
    - Phosphatidyl choline
    - Monobasic potassium phosphate
    - Dibasic sodium phosphate dihydrate
    - Sodium chloride
    - Potassium chloride

6.2 INCOMPATIBILITIES

This medicinal product must not be mixed with other medicinal products or be diluted.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

Unopened vial

The unopened vaccine is stored refrigerated at 2°C to 8°C, protected from light.

Unopened NUVAXOVID vaccine has been shown to be stable up to 12 hours at 25°C. Storage at 25°C is not the recommended storage or shipping condition.

Punctured vial

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 25°C.

From a microbiological point of view, after first opening (first needle puncture), the vaccine should be used immediately.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

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.

For storage conditions after first opening of the medicinal product, see section 6.3 Shelf Life.

6.5 NATURE AND CONTENTS OF CONTAINER

Multidose vial

5-dose vial

Each clear glass vial (type I glass) with a stopper (bromobutyl rubber) and an aluminium overseal with blue plastic flip-off cap contains 2.5 mL of suspension for injection.

Each clear glass vial contains 5 doses of 0.5 mL.

Pack size: 2 multidose vials or 10 multidose vials in a carton.

Not all pack sizes may be marketed.

10-dose vial

Each clear glass vial (type I glass) with a stopper (bromobutyl or chlorobutyl rubber) and an aluminium overseal with blue plastic flip-off cap contains 5 mL of suspension for injection.

Each clear glass vial contains 10 doses of 0.5 mL.

Pack size: 10 multidose vials in a carton.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicinal product or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Not applicable

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (Schedule 4)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

20 January 2022

10 DATE OF REVISION

26 October 2023

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.1 Indications	Removal of reference to Provisional approval
4.2 Dose and method of administration	Update of wording from booster to additional dose, add reference to ATAGI
4.8 Adverse effects	Update of section to reflect available study data
5.1 Pharmacodynamic properties	Update of section to reflect available study data
6.1 List of excipients	Editorial addition of ingredients
8 Sponsor	Update of sponsor details