▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Nuvaxovid dispersion for injection
COVID-19 Vaccine (recombinant, adjuvanted)

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).

One dose (0.5 mL) contains 5 micrograms of the SARS-CoV-2 spike protein* and is adjuvanted with Matrix-M.

Adjuvant Matrix-M containing per 0.5 mL dose: Fraction-A (42.5 micrograms) and Fraction-C (7.5 micrograms) of *Quillaja saponaria* Molina extract.

*produced by recombinant DNA technology using a baculovirus expression 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.

3. PHARMACEUTICAL FORM

Dispersion for injection (injection).

The dispersion is colourless to slightly yellow, clear to mildly opalescent (pH 7.2)

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Nuvaxovid is indicated for active immunisation to prevent 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 Posology and method of administration

Posology

Primary vaccination series
Individuals 12 years of age and older
Nuvaxovid is administered intramuscularly as a course of 2 doses of 0.5 mL each. It is recommended to administer the second dose 3 weeks after the first dose (see section 5.1).

Interchangeability
There are no data available on the interchangeability of Nuvaxovid with other COVID-19 vaccines to complete the primary vaccination course. Individuals who have received a first dose of Nuvaxovid should receive the second dose of Nuvaxovid to complete the vaccination course.

Booster dose
Booster dose in individuals 12 years of age and older
A booster dose of Nuvaxovid (0.5 mL) may be administered intramuscularly approximately 6 months after the primary series of Nuvaxovid in individuals 12 years of age and older *(*homologous booster dose*).*
Nuvaxovid may also be given as a booster dose in individuals 18 years of age and older following a primary series comprised of an mRNA vaccine or adenoviral vector vaccine (heterologous booster dose). The dosing interval for the heterologous booster dose is the same as that authorised for a booster dose of the vaccine used for primary vaccination (see section 5.1).

Paediatric population
The safety and efficacy of Nuvaxovid in children aged less than 12 years have not yet been established. No data are available.

Elderly population
No dose adjustment is required in elderly individuals ≥ 65 years of age.

Method of administration

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

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

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

For instructions on handling and disposal of the vaccine, see section 6.6.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Traceability

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

General recommendations

Hypersensitivity and anaphylaxis

Events of anaphylaxis have been reported with 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 following vaccination with Nuvaxovid. These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. (see section 4.8).

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. Vaccinees (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.

Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

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.

Excipients

Sodium
This vaccine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

Potassium
This vaccine contains potassium, less than 1 mmol (39 mg) per dose, that is to say, essentially ‘potassium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Co-administration of Nuvaxovid with inactivated influenza vaccines has been evaluated in a limited number of participants in an exploratory clinical trial sub-study, see section 4.8 and section 5.1.

The binding antibody response to SARS-CoV-2 was lower when Nuvaxovid was given concomitantly with inactivated influenza vaccine. The clinical significance of this is unknown.

Concomitant administration of Nuvaxovid with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/fetal development, parturition, or post-natal development (see section 5.3).

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

Breast-feeding

It is unknown whether Nuvaxovid is excreted in human milk.

Fertility

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

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 may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile after primary series

Participants 18 years of age and older
The safety of Nuvaxovid was evaluated from an interim analysis of pooled data from 5 ongoing clinical trials conducted in Australia, South Africa, the United Kingdom, the United States and Mexico. At the time of the analysis, a total of 49,950 participants aged 18 years and older received at least one dose of the two-dose primary series of Nuvaxovid (n=30,058) or placebo (n=19,892). 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 years and older enrolled in the two phase 3 studies who received any dose of Nuvaxovid (n=20,055) or placebo (n=10,561), the most frequent adverse reactions were injection site tenderness (75%), injection site pain (62%), fatigue (53%), myalgia (51%), headache (50%), malaise (41%), arthralgia (24%), and nausea or vomiting (15%). 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 tenderness, injection site pain, fatigue, myalgia, headache, malaise, arthralgia, and nausea or vomiting was higher in adults aged 18 to less than 65 years than in those aged 65 years and above.

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

Licensed inactivated seasonal influenza vaccines were co-administered to participants on the same day as Dose 1 of Nuvaxovid (n=217) or placebo (n=214) in the opposite deltoid muscle of the arm in 431 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.

Adolescents 12 through 17 years of age
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 through 17 years of age, with and without evidence of prior SARS CoV-2 infection, in United States who received at least one 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 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%). Fever was observed more frequently in adolescents aged 12 through to 17 years compared to 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.

Summary of the safety profile after booster dose

Participants 18 years of age and older
In an independent study (CoV-BOOST study, EudraCT 2021-002175-19) evaluating the use of a Nuvaxovid booster dose in individuals who had completed primary vaccination with an authorised mRNA COVID-19 vaccine or adenoviral vector COVID-19 vaccine, no new safety concerns were identified.

The safety and immunogenicity of a booster dose of Nuvaxovid was evaluated in an ongoing Phase 3, multicenter, randomized, observer-blinded, placebo-controlled study (Study 2019nCoV-301). Overall, 12,777 participants received a booster dose of the vaccine at least 6 months after the two-dose primary series (median of 11 months between completion of primary series and booster dose). Of the 12,777 participants who received a booster dose, 39 participants did not receive Nuvaxovid for all three doses. The 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=10,137).

The most frequent solicited adverse reactions were injection site tenderness (73%), injection site pain (61%), fatigue (52%), muscle pain (51.%), headache (45.%), malaise (40%), and joint pain (26.%).

Adolescents 12 through 17 years of age

The safety of a booster dose of Nuvaxovid was evaluated in an interim analysis of an ongoing Phase 3 study (Study 2019nCoV-301). A total of 1,499 participants received a booster dose approximately 9 months after receiving Dose 2 of the primary series. A subset of 220 participants who received the booster dose were evaluated for solicited adverse reactions within 7 days after the booster dose (Ad Hoc Booster Safety Analysis Set), of whom 190 completed the electronic diary.

Solicited adverse reactions occurred at higher frequencies and with higher grade in adolescents compared to adults. The most frequent solicited adverse reactions were injection site tenderness (72%), headache (68%), fatigue (66%), injection site pain (64%), muscle pain (62%), malaise (47%),

and nausea/vomiting (26%) 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.

Tabulated list of adverse reactions

Adverse reactions observed during clinical studies are listed below according to the following frequency categories:
Very common (≥ 1/10),
Common (≥ 1/100 to < 1/10),
Uncommon (≥ 1/1,000 to < 1/100),
Rare (≥ 1/10,000 to < 1/1,000),
Very rare (< 1/10,000),
Not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse reactions from Nuvaxovid clinical trials and post--authorisation experience 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)**	**Not known (cannot be estimated from the available data)**
Blood and lymphatic system disorders			Lymphadenopathy		
Immune system disorders					Anaphylaxis
Nervous system disorders	Headache				Paraesthesia Hypoaesthesia
Cardiac disorders					Myocarditis Pericarditis
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[e] Chills Pain in extremity	Injection site pruritus	Injection site warmth	

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 aged 12 through 17 years in the clinical study.

e Pyrexia was observed more frequently in adolescents aged 12 through 17 years compared to adults, with the frequency being very common after the second dose in adolescents.

Description of selected adverse reactions

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

Reporting of suspected adverse reactions

If you are concerned about an adverse event, it should be reported on a Yellow card. Reporting forms and information can be found at https://coronavirus-yellowcard.mhra.gov.uk or you can search for MHRA Yellow Card in the Google Play or Apple App Store. When reporting, please include the vaccine brand and batch/lot number, if available.

Alternatively, adverse events of concern in association with Nuvaxovid can be reported to Novavax at www.NovavaxCovidVaccine.com or via +44 020 3514 1838. Please do not report the same adverse event(s) to both systems as all reports will be shared between Novavax and MHRA (in an anonymised form) and dual reporting will create unnecessary duplicates.

4.9 Overdose

No case of overdose has been reported. In the event of an overdose, monitoring of vital functions and possible symptomatic treatment is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vaccine, protein subunit, ATC code: J07BN04

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 two vaccine components elicit B- and T-cell immune responses to the S protein, including neutralising antibodies, which may contribute to protection against COVID-19.

Clinical efficacy

Primary series

The clinical efficacy, safety, and immunogenicity of Nuvaxovid is being evaluated in two pivotal, placebo-controlled, Phase 3 studies, Study 1 (2019nCoV-301) conducted in North America and Study 2 (2019nCoV-302) conducted in the United Kingdom, and a Phase 2a/b study, Study 3, conducted in South Africa.

Study 1 (2019nCoV-301)
Study 1 is an ongoing Phase 3, multicentre, randomised, observer-blinded, placebo-controlled study with an adult main study conducted in participants 18 years of age and older in the United States and Mexico, and a paediatric 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 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 completed in February 2021. Participants will be followed for up to 24 months after the second dose for assessments of safety, and efficacy against COVID-19. Following collection of sufficient safety data to support application for emergency use authorisation, initial recipients of placebo were invited to receive two injections of Nuvaxovid 21 days apart and initial recipients of Nuvaxovid 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.

The primary efficacy analysis population (referred to as the Per-Protocol Efficacy [PP-EFF] analysis set) included 25,452 participants who received either Nuvaxovid (n = 17,312) or placebo (n = 8,140), received two doses (Dose 1 on day 0; Dose 2 at day 21, median 21 days [IQR 21-23], range 14-60), 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 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 human immunodeficiency virus (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.

COVID-19 cases were confirmed by polymerase chain reaction (PCR) through a central laboratory. Vaccine efficacy is presented in Table 2.

Table 2: Vaccine efficacy against PCR-confirmed COVID-19 with onset from 7 days after second vaccination [1] - PP-EFF analysis set; Study 2019nCoV-301

Subgroup	Nuvaxovid			Placebo			% Vaccine Efficacy (95% CI)
	Partici-pants N	COVID-19 cases n (%)[2]	Incidence Rate Per Year Per 1,000 People[2]	Partici-pants N	COVID-19 cases n (%)[3]	Incidence Rate Per Year Per 1,000 People[2]	
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)[3,4]

[1] VE evaluated in participants without major protocol deviations, who are seronegative (for SARS-CoV-2) at baseline and do not have a laboratory confirmed current SARS-CoV-2 infection with symptom onset up to 6 days after the second dose, and who have received the full prescribed regimen of trial vaccine.

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

[3] 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 VE = 100 × (1 – relative risk) (Zou 2004).

[4] Met primary efficacy endpoint criterion for success with a lower bound confidence interval (LBCI) > 30%. at the planned primary confirmatory analysis

Vaccine efficacy of Nuvaxovid to prevent the onset of COVID-19 from seven days after Dose 2 was 90.4% (95% CI 82.9, 94.6). No cases of severe COVID-19 were reported in the 17,312 Nuvaxovid participants compared with 4 cases of severe COVID-19 reported in the 8,140 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 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 (e.g., BMI $\geq$ 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 of Interest were predominantly circulating in the two 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 identified 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 through 17 years of age
The assessment of efficacy and immunogenicity of Nuvaxovid in adolescent participants 12 through 17 years of age occurred in the United States in the ongoing paediatric expansion portion of the Phase 3 multicentre, randomised, observer-blinded, placebo-controlled 2019nCoV-301 study. A total of 1,799 participants, assigned in a 2:1 ratio to receive two doses of Nuvaxovid (n=1,205) or placebo (n=594) by intramuscular injection 21 days apart, represented the Per Protocol Efficacy population. Participants with confirmed infection or prior infection due to SARSCoV-2 at the time of randomisation were not included in the primary efficacy analysis.

Enrolment of adolescents completed in June 2021. Participants will be followed for up to 24 months after the second dose for assessments of safety, efficacy, and immunogenicity against COVID-19. Following collection of a 60 days safety follow-up period, initial adolescent recipients of placebo were invited to receive two injections of Nuvaxovid 21 days apart and initial recipients of Nuvaxovid 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.

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 COVD-19 symptoms.

There were 20 cases of PCR-confirmed symptomatic mild COVID-19 (Nuvaxovid, 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%).

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%).

Immunogenicity in adolescents 12 through 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) and PCR-negative at baseline. Neutralising antibody responses were compared with those observed in seronegative/PCR-negative adult participants aged 18 through 25 years from the adult main study (Per Protocol Immunogenicity (PP-IMM) Analysis Set) as shown in Table 3. Noninferiority required that the following three criteria were met: lower bound of two-sided 95% CI for the ratio of geometric

mean titers (GMTs) (GMT 12 through 17 years/GMT 18 through 25 years) > 0.67; point estimate of the ratio of GMTs ≥ 0.82; and the lower bound of the two-sided 95% CI for difference of seroconversion rates (SCRs) (SCR 12 through 17 years minus SCR 18 through 25 years) > -10%. These noninferiority criteria were met.

Table 3: **Adjusted Ratio of Geometric Mean of Microneutralisation Assay Neutralising Antibody Titers for SARS-CoV-2 S Wild-Type Virus at Day 35 Overall and Presented by Age Group (PP-IMM Analysis Set)[1]**

Assay	Timepoint	Paediatric Expansion (12 through 17 Years) N=390	Adult Main Study (18 through 25 Years) N=416	12 through 17 Years versus 18 through 25 Years
		GMT 95% CI[2]	GMT 95% CI[2]	GMR 95% CI[2]
Microneutralisation (1/dilution)	Day 35 (14 days after Dose 2)	3859.6 (3422.8, 4352.1)	2633.6 (2388.6, 2903.6)	1.46 (1.25, 1.71)[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; MN = microneutralisation; 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 coronavirus 2.

[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 through 25 years) with non-missing neutralising antibodies result
n2 = number of participants in paediatric expansion (12 through 17 years) with non-missing neutralising antibodies result

Study 2 (2019nCoV-302)

Study 2 is an ongoing Phase 3, multicentre, randomised, 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) 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 hospitalisation 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 are being followed for up to 12 months after the primary vaccination series for assessments of safety and efficacy against COVID-19.

The primary efficacy analysis set (PP-EFF) included 14,039 participants who received either Nuvaxovid (n=7,020) or placebo (n=7,019), received two 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, 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 one comorbid condition.

Table 4: 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% (79.7, 94.9)[2]
65 to 84 years of age	1,953	1 (0.10)[2]	---	1,957	9 (0.9)[2]	---	88.9% (20.2, 99.7)[4]

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

[2] 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 [Zou 2004].

[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.1.1.7 (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.

Licensed seasonal influenza vaccine co-administration sub-study
Overall, 431 participants were co-vaccinated with inactivated seasonal influenza vaccines; 217 sub-study participants received Nuvaxovid and 214 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 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 one 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-spike IgG assay with seroconversion rates similar to participants who did not receive concomitant influenza vaccine (see section 4.5 and section 4.8).

Study 3 (2019nCoV-501)
Study 3 is an ongoing Phase 2a/b, multicentre, 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.

Enrolment was completed in November 2020.

The primary efficacy analysis set (PP-EFF) included 2,770 participants who received either Nuvaxovid (n=1,408) or placebo (n=1,362), received two 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 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, 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 (3.62%) cases for Nuvaxovid versus 96 (7.05%) 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.

Booster dose

Immunogenicity in participants 18 years of age and older
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 254 participants (Full Analysis Set) received two doses of Nuvaxovid (0.5 mL, 5 micrograms 3 weeks apart) as the primary vaccination series. A subset of 104 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 96-fold increase in neutralising antibodies from a GMT of 63 pre-booster (Day 189) to a GMT of 6,023 post-booster (Day 217) and an approximate 4.1-fold increase from a peak GMT (14 days post-Dose 2) of 1,470.

Study 2019nCoV-501
In Study 3, an ongoing 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). An approximate 52-fold increase in neutralising antibodies was shown from a GMT of 69 pre-booster (Day 201) to a GMT of 3,600 post-booster (Day 236) and an approximate 5.2-fold increase from a peak GMT (14 days post-Dose 2) of 694.

Safety and immunogenicity of COVID-19 vaccines given as a third dose (booster) following completion of a primary vaccination series with another authorised COVID-19 vaccine in the UK.

An independent, multicentre, randomised, controlled, Phase 2 investigator-initiated trial (CoV-BOOST, EudraCT 2021-002175-19) investigated the immunogenicity of a third dose (booster) in adults aged 30 years and older with no history of laboratory-confirmed SARS-CoV-2 infection. Nuvaxovid was 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. Neutralising antibody titers measured by a wild-type assay were assessed 28 days post-booster dose. Within the group assigned to receive Nuvaxovid, 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 (0.5 mL) of Nuvaxovid. Nuvaxovid demonstrated a booster response regardless of the vaccine used for primary vaccination.

Booster dose in Adolescents 12 through 17 years of age

The effectiveness of booster doses of Nuvaxovid in adolescents 12 through 17 years of age is inferred from data gathered for booster doses of the vaccine in adults in studies 2019nCoV-101 and 2019nCoV-501, as Nuvaxovid has been shown to induce a comparable immune response and effectiveness after the primary series in adolescents as in adults, and the ability to boost the vaccine-induced immune response was shown in adults.

Elderly population

Nuvaxovid was assessed in individuals 18 years of age and older. The efficacy of Nuvaxovid was consistent between elderly (≥ 65 years) and younger individuals (18 to 64 years) for the primary series.

Paediatric population

The licensing authority has deferred the obligation to submit the results of studies with Nuvaxovid in one or more subsets of the paediatric population in prevention of COVID-19, see section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium hydrogen phosphate heptahydrate
Sodium dihydrogen phosphate monohydrate
Sodium chloride
Polysorbate 80
Sodium hydroxide (for adjustment of pH)
Hydrochloric acid (for adjustment of pH)
Water for injections

Adjuvant (Matrix-M)
Cholesterol
Phosphatidylcholine (including all-rac-α-Tocopherol)
Potassium dihydrogen phosphate
Potassium chloride
Disodium hydrogen phosphate dihydrate
Sodium chloride
Water for injections

For adjuvant: see also section 2.

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial

12 months 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 but may guide decisions for use in case of temporary temperature excursions during the 12-month storage at 2°C to 8°C.

Punctured vial

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

From a microbiological point of view, after first opening (first needle puncture), the vaccine should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and should not exceed 12 hours at 2°C to 8°C or 6 hours at room temperature (maximum 25°C).

6.4 Special precautions for storage

Store in a refrigerator (2°C - 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.

6.5 Nature and contents of container

Multidose vial

5-dose vial
2.5 mL of dispersion in a vial (type I glass) with a stopper (bromobutyl rubber) and an aluminium overseal with blue plastic flip-off cap.

Each vial contains 5 doses of 0.5 mL.

Pack size: 2 multidose vials or 10 multidose vials

10-dose vial
5 mL of dispersion in a vial (type I glass) with a stopper (bromobutyl rubber) and an aluminium overseal with blue plastic flip-off cap.

Each vial contains 10 doses of 0.5 mL.

Pack size: 2 multidose vials or 10 multidose vials

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Handling instructions and administration

This vaccine should be handled by a healthcare professional using aseptic techniques to ensure the sterility of each dose.

Preparation for use

- The vaccine comes ready to use.
- Unopened vaccine should be stored at 2°C to 8°C and kept within the outer carton to protect from light.
- Immediately prior to use, remove the vaccine vial from the carton in the refrigerator.
- Record the date and time of discard on the vial label. Use within 12 hours after first puncture.

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 dispersion 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 5 doses (vial of 2.5 mL) or 10 doses (vial of 5mL) 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.
    - 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

- Store the opened vial between 2°C to 8°C for up to 12 hours or at room temperature (maximum 25°C) for up to 6 hours after first puncture, see section 6.3.

Discard

- Discard this vaccine if not used within 12 hours when stored between 2°C to 8°C or 6 hours when stored at room temperature after first puncture of the vial, see section 6.3.

Disposal

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

7. MARKETING AUTHORISATION HOLDER

Novavax CZ a.s.
Bohumil 138
Jevany, 28163

Czechia

8. MARKETING AUTHORISATION NUMBER(S)

PLGB 54180/0002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: February 2022
Date of latest renewal: 11 January 2023

10. DATE OF REVISION OF THE TEXT

17 November 2023