ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼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 3 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.

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

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. An additional dose of the vaccine should not be given to those who have experienced anaphylaxis to a prior 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 less than 1 mmol potassium (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/foetal 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 foetus.

Breast-feeding

It is unknown whether Nuvaxovid is excreted in human milk.

No effects on the breast-fed newborn/infant are anticipated since the systemic exposure of the breast-feeding woman to Nuvaxovid is negligible.

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity, see section 5.3.

4.7 Effects on ability to drive and use machines

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 most frequent adverse reactions after administration of a Nuvaxovid dose within the primary series were injection site tenderness (75%), injection site pain (62%), fatigue (53%), myalgia (51%),

headache (50%), malaise (41%), arthralgia (24%), and nausea or vomiting (14%). 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: 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.

Following co-administration with seasonal influenza vaccine, higher frequencies of local adverse reactions at the Nuvaxovid injection site (70.1% after Dose 1 and 85.0% after Dose 2) and systemic adverse reactions (60.1% after Dose 1 and 69.7 after Dose 2) have been observed.

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
The most frequent adverse reactions reported following receipt of a booster dose of Nuvaxovid after the two-dose primary series were injection site tenderness (73%), injection site pain (61%), fatigue (53%), muscle pain (52%), headache (46%), malaise (41%), 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

Unless otherwise stated the frequency categories are based on the safety of Nuvaxovid assessed in 5 clinical trials with a total of 30,070 participants aged 18 years and older who received at least one dose of the two-dose primary series of Nuvaxovid (the median duration of follow-up was 84 days post-Dose 2) and one clinical trial in which 13,354 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).

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] Pain in extremity	Injection site pruritus Chills	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

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V and include batch/Lot number if available.

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 was a 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; had 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 were 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 conditional marketing 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 24,784 participants who received either Nuvaxovid (n = 16,898) or placebo (n = 7,886), received two doses (Dose 1 on day 0; Dose 2 at day 21, median 21 days [IQR 21-23], range 20-60), 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 = 14,908) were 18 to 64 years old and 12% (n = 1,990) 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 16,100 (95%) participants. Comorbidities included: obesity (body mass index (BMI) $\geq$ 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 $\geq$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	16,880	18 (0.1)	3.36	7,814	72 (0.9)	39.74	91.53% (83.31, 95.70)[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 91.53% (95% CI: 83.31, 95.70). No cases of severe COVID-19 were reported in the 16,880

Nuvaxovid participants compared with 4 cases of severe COVID-19 reported in the 7,886 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 Being Monitored were predominantly circulating in the two countries (US and Mexico) where the study was conducted. Sequencing data were available for 70 of the 90 endpoint cases (78%). Of these, 54 out of 70 (77%) were identified as Variants of Concern or Variants Being Monitored. The most common Variants of Concern/Variants Being Monitored identified were Alpha with 52/90 cases (58%), Beta (2/90, 2%), Gamma (3/90, 3%), Iota with 9/90 cases (10%), and Epsilon (19/90, 21%).

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 SARS-CoV-2 at the time of randomisation were not included in the primary efficacy analysis.

Enrolment of adolescents completed in June 2021. Participants were followed for up to 24 months after the second dose for assessments of safety, efficacy, and immunogenicity against COVID-19. Following a 60-day 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 COVID-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. Non-inferiority 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 $\geq$ 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 non-inferiority 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 was a 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 were 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 13,971 participants who received either Nuvaxovid (n=6,979) or placebo (n=6,992), 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 (Table 4).

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=5,039) were 18 to 64 years old and 28% (n=1,940) were aged 65 to 84; 49% were female; 95% 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.

Vaccine efficacy of Nuvaxovid to prevent the onset of COVID-19 from 7 days after Dose 2 was 87.2% (95% CI: 78.1, 92.5). No cases of severe COVID-19 were reported in the 6,979 Nuvaxovid

participants compared with 6 cases of severe COVID-19 reported in the 6,992 placebo recipients in the PP-EFF analysis set.

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	6,979	15 (0.2)	9.47	6,992	116 (1.7)	73.88	87.2% (78.1, 92.5)[2,3]
Subgroup analyses of the primary efficacy endpoint							
18 to 64 years of age	5,039	13 (0.3)	18.86	5,042	108 (2.1)	158.12	88.1% (79.7, 94.9)[2]
65 to 84 years of age	1,940	2 (0.1)[2]	7.08	1,950	8 (0.4)[2]	28.33	75.0% (-25.3, 97.4)[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 118 of the 131 endpoint cases (90%). Of these, 80 out of 118 (68%) were identified as the Alpha variant with the other cases classified as non-Alpha.

Licensed seasonal influenza vaccine co-administration sub-study
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=190), median age was 40 years (range: 22 to 70 years); 94% (n=178) were 18 to 64 years old and 6% (n=12) were aged 65 to 84; 43% were female; 86% were White; 14% 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 was a 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 2,769 participants who received either Nuvaxovid (n=1,413) or placebo (n=1,356), 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); 39% were female; 94% were Black/African American; 5% were White; 3% were multiple races, 1% were Asian; and 2% were Hispanic or Latino; and 5.4% were HIV-positive.

A total of 168 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 57 (4.0%) cases for Nuvaxovid versus 111 (8.2%) cases for placebo. The resultant vaccine efficacy of Nuvaxovid was 50.7% (95% CI: 32.8, 63.9).

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 a 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 84.8-fold increase in neutralising antibodies from a GMT of 68.3 pre-booster (Day 189) to a GMT of 5,834.3 post-booster (Day 217) and an approximate 6.8-fold increase from a peak GMT (14 days post-Dose 2) of 855.2.

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 1,169 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 52.2-fold increase in neutralising antibodies was shown from a GMT of 69 pre-booster (Day 201) to a GMT of 3,603 post-booster (Day 236) and an approximate 5.2-fold increase from a peak GMT (14 days post-Dose 2) of 690.

Safety and immunogenicity of COVID-19 vaccines given as booster doses following completion of a primary vaccination series with another authorised COVID-19 vaccine was evaluated in an independent study in the UK.

The independent, multicentre, randomised, controlled, Phase 2 investigator-initiated trial (CoV-BOOST, EudraCT 2021-002175-19) investigated the immunogenicity of a 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 European Medicines Agency 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 and reproductive and developmental toxicity.

Genotoxicity and Carcinogenicity

In vitro genotoxicity studies were conducted with the Matrix-M adjuvant. The adjuvant was shown to be non-genotoxic. Carcinogenicity studies were not performed. Carcinogenicity is not expected.

Reproductive toxicity

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

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

9 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 9-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 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.

- 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

Sanofi Winthrop Industrie
82 Avenue Raspail
94250 Gentilly
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1618/001	10 multidose vials (10 doses per vial)
EU/1/21/1618/002	10 multidose vials (5 doses per vial)
EU/1/21/1618/003	2 multidose vials (10 doses per vial)
EU/1/21/1618/004	2 multidose vials (5 doses per vial)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 December 2021
Date of latest renewal: 03 October 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

▼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 XBB.1.5 dispersion for injection
COVID-19 Vaccine (recombinant, adjuvanted)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

These are single dose vials or multidose vials.

One single dose vial contains 1 dose of 0.5 mL, see section 6.5.

One multidose vial contains 5 doses of 0.5 mL per vial, see section 6.5.

One dose (0.5 mL) contains 5 micrograms of the SARS-CoV-2 (Omicron XBB.1.5) 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 XBB.1.5 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

Nuvaxovid XBB.1.5 is administered intramuscularly as a single dose (0.5 mL) for individuals 12 years of age and older regardless of previous vaccination status.

For individuals who have previously been vaccinated with a COVID-19 vaccine, Nuvaxovid XBB.1.5 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Immunocompromised individuals
Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations, see section 4.4.

Paediatric population
The safety and efficacy of Nuvaxovid XBB.1.5 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 XBB.1.5 is for intramuscular injection only, preferably into the deltoid muscle of the upper arm.

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

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. An additional dose of the vaccine should not be given to those who have experienced anaphylaxis to a prior 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 XBB.1.5 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 vaccination. As with all vaccines, vaccination with Nuvaxovid XBB.1.5 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 less than 1 mmol potassium (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 (Original, Wuhan strain) 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 XBB.1.5 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/foetal development, parturition, or post-natal development, see section 5.3.

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

Breast-feeding

It is unknown whether Nuvaxovid XBB.1.5 is excreted in human milk.

No effects on the breast-fed newborn/infant are anticipated since the systemic exposure of the breast-feeding woman to Nuvaxovid XBB.1.5 is negligible.

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity, see section 5.3.

4.7 Effects on ability to drive and use machines

Nuvaxovid XBB.1.5 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

Nuvaxovid (Original, Wuhan strain)

Summary of the safety profile after primary series

Participants 18 years of age and older
The most frequent adverse reactions after administration of a Nuvaxovid dose within the primary series were injection site tenderness (75%), injection site pain (62%), fatigue (53%), myalgia (51%), headache (50%), malaise (41%), arthralgia (24%), and nausea or vomiting (14%). 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: 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.

Following co-administration with seasonal influenza vaccine, higher frequencies of local adverse reactions at the Nuvaxovid injection site (70.1% after Dose 1 and 85.0% after Dose 2) and systemic adverse reactions (60.1% after Dose 1 and 69.7 after Dose 2) have been observed.

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

The most frequent adverse reactions reported following receipt of a booster dose of Nuvaxovid after the two-dose primary series were injection site tenderness (73%), injection site pain (61%), fatigue (53%), muscle pain (52%), headache (46%), malaise (41%), 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.

Nuvaxovid XBB.1.5 (Omicron-adapted Nuvaxovid)

The safety of Nuvaxovid XBB.1.5 is inferred from the safety data of the Nuvaxovid (Original, Wuhan strain) vaccine and the safety data from the adapted Omicron BA.5 vaccine.

A booster dose of the Nuvaxovid monovalent Omicron BA.5 and bivalent Original/Omicron BA.5 vaccines were evaluated in an ongoing Phase 3 study in participants 18 years of age and older (2019nCoV-311 Part 2). In this study, 251 participants received a Nuvaxovid (Original, Wuhan strain) booster dose, 254 received a monovalent Omicron BA.5 booster dose, and 259 participants received a

Nuvaxovid bivalent Original/Omicron BA.5 booster dose. Median follow-up time since the initial booster vaccination was 48 days through the data cutoff date of 31 May 2023.

The overall safety profile for the Nuvaxovid monovalent Omicron BA.5 booster doses was similar to that seen after the Nuvaxovid (Original, Wuhan strain) booster dose. The most frequent adverse reactions were injection site tenderness (> 50%), injection site pain (> 30%), fatigue (> 30%), headache (> 20%), myalgia (> 20%), and malaise (> 10%). No new adverse reactions were identified for the Nuvaxovid monovalent Omicron BA.5 booster doses. In 2019nCoV-311 Part 2 the frequency of local as well as systemic reactogenicity events was greater in women than in men, for all the vaccine constructs that were tested.

Tabulated list of adverse reactions

Unless otherwise stated the frequency categories are based on the safety of Nuvaxovid assessed in 5 clinical trials with a total of 30,070 participants aged 18 years and older who received at least one dose of the two-dose primary series of Nuvaxovid (the median duration of follow-up was 84 days post-Dose 2) and one clinical trial in which 13,354 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).

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		

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)
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] Pain in extremity	Injection site pruritus Chills	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

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V and include batch/Lot number if available.

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 XBB.1.5 is composed of purified full-length SARS-CoV-2 Omicron XBB.1.5 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.

Nuvaxovid XBB.1.5 (Omicron-adapted Nuvaxovid)

The efficacy of Nuvaxovid XBB.1.5 is inferred from the efficacy data of the Nuvaxovid (Original, Wuhan strain) vaccine and immunogenicity data from the adapted vaccine of the Omicron BA.5 strain.

In study 2019nCoV-311 Part 2, a total of 694 participants 18 years of age and older, who were evaluated for immunogenicity and previously received 3 or more doses of the Pfizer-BioNTech COVID-19 vaccine or the Moderna COVID-19 vaccine received 1 of the following as a booster dose: Nuvaxovid (Original, Wuhan strain), Nuvaxovid monovalent Omicron BA.5 vaccine or Nuvaxovid bivalent Original/Omicron BA.5 vaccine. The booster doses were administered a median of 11 – 13 months after the last vaccination, respectively. GMRs and seroresponse rates were evaluated at 1 month after vaccination.

The primary objective of the study was to demonstrate superiority with respect to level of pseudovirus neutralizing antibody titer (ID_{50}) and non-inferiority with respect to seroresponse rate of the anti-Omicron BA.5 immune response induced by a dose of the Nuvaxovid bivalent Original/Omicron BA.5 vaccine relative to the response elicited by a dose of Nuvaxovid (Original, Wuhan strain), and to assess non-inferiority with respect to level of ID_{50} for the original SAR-CoV-2 strain for the Nuvaxovid bivalent Original/Omicron BA.5 vaccine compared to Nuvaxovid (Original, Wuhan strain).

Superiority of the anti-Omicron BA.5 ID_{50} for the Nuvaxovid bivalent Original/Omicron BA.5 vaccine relative to Nuvaxovid (Original, Wuhan strain) was demonstrated, as the lower bound of the two-sided 95% confidence interval (CI) for GMR was >1. Non-inferiority of the anti-Original ID_{50} for the Nuvaxovid bivalent Original/Omicron BA.5 vaccine relative to Nuvaxovid (Original, Wuhan strain) was met, as the lower bound of the two-sided 95% CI for GMR was >0.67.
Non-inferiority of the seroresponse rate to the Omicron BA.5 variant for the Nuvaxovid bivalent Original/Omicron BA.5 vaccine relative to Nuvaxovid (Original, Wuhan strain) was met, as the lower limit of the two-sided 95% CI for the difference in percentages of participants with seroresponse was >-5%. For more details see Table 2.

Exploratory immunogenicity analyses included an assessment of the ID_{50} GMT ratio and difference in seroresponse rates for the Nuvaxovid monovalent Omicron BA.5 vaccine compared to Nuvaxovid (Original, Wuhan strain). The GMT ratio following the booster dose with Nuvaxovid monovalent Omicron BA.5 vaccine compared with the booster dose of Nuvaxovid (Original, Wuhan strain) was 2.5 (two-sided 95% CIs: 2.10, 2.94). The difference in seroresponse rates between the booster dose with Nuvaxovid monovalent Omicron BA.5 vaccine and the booster dose with Nuvaxovid (Original, Wuhan strain) was 33.2% (two-sided 95% CIs: 25.4%, 40.7%). While not formally assessed, these responses would have met the three success criteria for the study.

Table 2: Omicron BA.5 and Wuhan pseudovirus neutralising antibody titres (ID_{50}) and seroresponse rates following booster vaccination with Nuvaxovid monovalent BA.5 vaccine, Nuvaxovid (Original, Wuhan strain), and Nuvaxovid bivalent Original/Omicron BA.5 Vaccine – PP pseudovirus neutralization assay subset; Study 2019nCoV-311 Part 2

Parameters	**Participants ≥ 18 Years**					
	Nuvaxovid Monovalent Omicron BA.5	**Nuvaxovid (Original, Wuhan strain)**	**Nuvaxovid Bivalent Original/Omicron BA.5**	**Bivalent vs. Original Fulfillment of hypothesis testing**	**Monovalent Omicron BA.5 vs. Original**	**Monovalent Omicron BA.5 vs. Bivalent**
Omicron BA.5 Pseudovirus neutralisation						
Baseline[1]						
n1	236	227	231			
GMT (ID_{50})	**348.4**	**326.6**	**293.3**			
95% CI[2]	283.9, 427.6	260.0, 410.4	237.3, 362.6			
Day 28						
n1	235	227	231	**GMTR,** LB of 95% CI > 1.0 criterion for superiority		
Adjusted GMT[3]	**1279.1**	**515.1**	**1017.8**	2.0 **YES**	2.5 NT	1.3 NT
95% CI[2]	1119.7, 1461.1	450.4, 589.0	891.0, 1162.6	1.69, 2.33	2.10, 2.94	1.06, 1.50
GMFR referencing Day 0	**4.4**	**1.8**	**3.6**			
95% CI[2]	3.8, 5.1	1.6, 2.0	3.2, 4.2	Difference in SRR[6] LB of 95% CI > -5% criterion for non-inferiority		
SRR ≥ 4-fold increase,[4] n3/n2 (%)	107/235 (**45.5**)	28/227 (**12.3**)	92/231 (**39.8**)	27.5 **YES**	33.2 NT	5.7 NT
95% CI[5]	39.0, 52.1	8.4, 17.3	33.5, 46.5	19.8, 35.0	25.4, 40.7	-3.3, 14.6
Ancestral (Wuhan) Pseudovirus neutralisation						
Baseline[1]						
n1	236	227	230			
GMT (ID_{50})	1355.4	1259.7	1222.1			
95% CI[2]	1141.7, 1609.2	1044.1, 1519.8	1024.5, 1457.9			
Day 28						
n1	236	227	231	**GMTR** LB of 95% CI > 0.67 criterion for non-inferiority		
Adjusted GMT[3]	2010.2	2205.6	2211.1	1.0 **YES**	0.9	0.9
95% CI[2]	1766.6, 2310.1	1926.4, 2525.1	1932.9, 2529.3	0.84, 1.20	0.78, 1.08	0.77, 1.09

GMFR referencing Day 0	1.6	1.9	1.9			
95% CI[2]	1.4, 1.9	1.6, 2.1	1.6, 2.2	Difference in SRR[6]		
SRR ≥ 4-fold increase,[4] n3/n2 (%)	53/236 (22.5)	52/227 (22.9)	54/230 (23.5)	0.6	-0.4	-1.0
95% CI[5]	17.3, 28.3	17.6, 28.9	18.2, 29.5	-7.2, 8.3	-8.1, 7.2	-8.7, 6.6

Abbreviations: CI = confidence interval; GMFR = geometric mean fold rise; GMT = geometric mean titre; GMTR = geometric mean titre ratio; ID_{50} = 50% inhibitory dilution; LB = lower bound; LLOQ = lower limit of quantitation; n1 = number of participants in the assay-specific PP-IMM analysis set within each visit with non-missing data; n2 = number of participants in the assay-specific PP-IMM analysis set with non-missing data at both day 0 and day 28; n3 = number of participants who reported ≥ 4-fold increase with percentages calculated based on n2 as the denominator; NT = not tested; PP-IMM = per-protocol immunogenicity; SRR = seroresponse rate.

1 Baseline was defined as the last non-missing assessment prior to booster vaccination.

2 The 95% CI for GMT and GMFR were calculated based on the t-distribution of the log-transformed values then back transformed to the original scale for presentation.

[3] An ANCOVA with vaccine group and age group (18-54, ≥ 55 years) as fixed effects and baseline value (Day 0) as covariate was performed that included all vaccine groups to estimate the adjusted GMT for all vaccine groups. Each pairwise comparison included the data from two groups only to estimate the adjusted GMTR between the two vaccine groups. The mean difference between vaccine groups and the corresponding CI limits was then exponentiated to obtain the ratio of ID_{50} GMTs and the corresponding 95% CIs.

[4] The SRR was defined as percentage of participants at each post vaccination visit with a titer ≥ 4-fold rise in ID_{50} level from baseline if the baseline value is equal or above LLOQ or ≥ 4-fold times the LLOQ if the baseline value is below the LLOQ and calculated based on n2 as the denominator.

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

[6] 95% CI for the difference in SRR was calculated based on the method of Miettinen and Nurminen.

Nuvaxovid (Original, Wuhan strain)

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 was a 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; had 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 were 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 conditional marketing 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 24,784 participants who received either Nuvaxovid (n = 16,898) or placebo (n = 7,886), received two doses (Dose 1 on day 0; Dose 2 at day 21, median 21 days [IQR 21-23], range 20-60), 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 = 14,908) were 18 to 64 years old and 12% (n = 1,990) 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 16,100 (95%) participants. Comorbidities included: obesity (body mass index (BMI) $\geq$ 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 $\geq$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 3.

Table 3: 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	16,880	18 (0.1)	3.36	7,814	72 (0.9)	39.74	91.53% (83.31, 95.70)[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 91.53% (95% CI: 83.31, 95.70). No cases of severe COVID-19 were reported in the 16,880 Nuvaxovid participants compared with 4 cases of severe COVID-19 reported in the 7,886 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 ≥ 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 two countries (US and Mexico) where the study was conducted. Sequencing data were available for 70 of the 90 endpoint cases (78%). Of these, 54 out of 70 (77%) were identified as Variants of Concern or Variants Being Monitored. The most common Variants of Concern/Variants Being Monitored identified were Alpha with 52/90 cases (58%), Beta (2/90, 2%), Gamma (3/90, 3%), Iota with 9/90 cases (10%), and Epsilon (19/90, 21%).

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 SARS-CoV-2 at the time of randomisation were not included in the primary efficacy analysis.

Enrolment of adolescents completed in June 2021. Participants were followed for up to 24 months after the second dose for assessments of safety, efficacy, and immunogenicity against COVID-19. Following a 60-day 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 COVID-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 4. Non-inferiority 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 non-inferiority criteria were met.

Table 4: **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 was a 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 were 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 13,971 participants who received either Nuvaxovid (n=6,979) or placebo (n=6,992), 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 (Table 5).

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=5,039) were 18 to 64 years old and 28% (n=1,940) were aged 65 to 84; 49% were female; 95% 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.

Vaccine efficacy of Nuvaxovid to prevent the onset of COVID-19 from 7 days after Dose 2 was 87.2% (95% CI: 78.1, 92.5). No cases of severe COVID-19 were reported in the 6,979 Nuvaxovid

participants compared with 6 cases of severe COVID-19 reported in the 6,992 placebo recipients in the PP-EFF analysis set.

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 (Original, Wuhan strain)			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	6,979	15 (0.2)	9.47	6,992	116 (1.7)	73.88	87.2% (78.1, 92.5)[2, 3]
Subgroup analyses of the primary efficacy endpoint							
18 to 64 years of age	5,039	13 (0.3)	18.86	5,042	108 (2.1)	158.12	88.1% (78.8, 93.3)[2]
65 to 84 years of age	1,940	2 (0.1)[2]	7.08	1,950	8 (0.4)[2]	28.33	75.0% (-25.3, 97.4)[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 118 of the 131 endpoint cases (90%). Of these, 80 out of 118 (68%) were identified as the Alpha variant with the other cases classified as non-Alpha.

Licensed seasonal influenza vaccine co-administration sub-study
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=190), median age was 40 years (range: 22 to 70 years); 94% (n=178) were 18 to 64 years old and 6% (n=12) were aged 65 to 84; 43% were female; 86% were White; 14% 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 was a 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 2,769 participants who received either Nuvaxovid (n=1,413) or placebo (n=1,356), 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); 39% were female; 94% were Black/African American; 5% were White; 3% were multiple races, 1% were Asian; and 2% were Hispanic or Latino; and 5.4% were HIV-positive.

A total of 168 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 57 (4.0%) cases for Nuvaxovid versus 111 (8.2%) cases for placebo. The resultant vaccine efficacy of Nuvaxovid was 50.7% (95% CI: 32.8, 63.9).

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 a 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 84.8-fold increase in neutralising antibodies from a GMT of 68.3 pre-booster (Day 189) to a GMT of 5,834.3 post-booster (Day 217) and an approximate 6.8-fold increase from a peak GMT (14 days post-Dose 2) of 855.2.

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 1,169 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 52.2-fold increase in neutralising antibodies was shown from a GMT of 69 pre-booster (Day 201) to a GMT of 3,603 post-booster (Day 236) and an approximate 5.2-fold increase from a peak GMT (14 days post-Dose 2) of 690.

Safety and immunogenicity of COVID-19 vaccines given as booster doses following completion of a primary vaccination series with another authorised COVID-19 vaccine was evaluated in an independent study in the UK.

The independent, multicentre, randomised, controlled, Phase 2 investigator-initiated trial (CoV-BOOST, EudraCT 2021-002175-19) investigated the immunogenicity of a 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 (Original, Wuhan strain) 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 European Medicines Agency 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 and reproductive and developmental toxicity.

Genotoxicity and Carcinogenicity

In vitro genotoxicity studies were conducted with the Matrix-M adjuvant. The adjuvant was shown to be non-genotoxic. Carcinogenicity studies were not performed. Carcinogenicity is not expected.

Reproductive toxicity

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

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

9 months at 2°C to 8°C, protected from light.

Unopened Nuvaxovid XBB.1.5 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 9-month storage at 2°C to 8°C.

Punctured multidose 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).

Punctured single dose vial

From a microbiological point of view, after the opening, the vaccine should be used immediately.
The single dose vial should be discarded after one dose withdrawal and administration, see section 6.6.

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

Single dose vial

0.5 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 one dose of 0.5 mL.

Pack size: 1 single dose vial or 10 single dose vials

Multidose 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

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.
- Single dose vial
    - Discard the vial and any excess volume after one 0.5 mL dose withdrawal and administration.
- Multidose vial
    - Use within 12 hours at 2°C to 8°C or 6 hours at room temperature (maximum 25°C) after first needle puncture. Record the date and time of discard on the vial label.

Inspect the vial

- Gently swirl the vial before the dose withdrawal. Do not shake. Gently swirl the multidose vial before each additional dose withdrawal.
- Each 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 one dose of 0.5 mL from the single dose vial or a maximum of 5 doses of 0.5 mL from the multidose vial (vial of 2.5 mL) 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 of multidose vial

- Store the opened multidose 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

- Single dose vial
    - Discard the vial and any excess volume after one dose withdrawal and administration.
- Multidose vial
    - 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 needle 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

Sanofi Winthrop Industrie
82 Avenue Raspail
94250 Gentilly
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1618/005	10 single dose vials (1 dose per vial)
EU/1/21/1618/006	10 multidose vials (5 doses per vial)
EU/1/21/1618/008	2 multidose vials (5 doses per vial)
EU/1/21/1618/010	1 single dose vial (1 dose per vial)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 December 2021
Date of latest renewal: 03 October 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

▼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 JN.1 dispersion for injection
COVID-19 Vaccine (recombinant, adjuvanted)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

These are single dose vials.

One single dose vial contains 1 dose of 0.5 mL, see section 6.5.

One dose (0.5 mL) contains 5 micrograms of the SARS-CoV-2 (Omicron JN.1) 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 JN.1 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

Nuvaxovid JN.1 is administered intramuscularly as a single dose (0.5 mL) for individuals 12 years of age and older regardless of previous vaccination status.

For individuals who have previously been vaccinated with a COVID-19 vaccine, Nuvaxovid JN.1 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Immunocompromised individuals
Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations, see section 4.4.

Paediatric population
The safety and efficacy of Nuvaxovid JN.1 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 JN.1 is for intramuscular injection only, preferably into the deltoid muscle of the upper arm.

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

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. An additional dose of the vaccine should not be given to those who have experienced anaphylaxis to a prior 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 JN.1 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 vaccination. As with all vaccines, vaccination with Nuvaxovid JN.1 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 less than 1 mmol potassium (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 (Original, Wuhan strain) 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 JN.1 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/foetal development, parturition, or post-natal development, see section 5.3.

Administration of Nuvaxovid JN.1 in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and foetus.

Breast-feeding

It is unknown whether Nuvaxovid JN.1 is excreted in human milk.

No effects on the breast-fed newborn/infant are anticipated since the systemic exposure of the breast-feeding woman to Nuvaxovid JN.1 is negligible.

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity, see section 5.3.

4.7 Effects on ability to drive and use machines

Nuvaxovid JN.1 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

Nuvaxovid (Original, Wuhan strain)

Summary of the safety profile after primary series

Participants 18 years of age and older
The most frequent adverse reactions after administration of a Nuvaxovid dose within the primary series were injection site tenderness (75%), injection site pain (62%), fatigue (53%), myalgia (51%), headache (50%), malaise (41%), arthralgia (24%), and nausea or vomiting (14%). 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: 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.

Following co-administration with seasonal influenza vaccine, higher frequencies of local adverse reactions at the Nuvaxovid injection site (70.1% after Dose 1 and 85.0% after Dose 2) and systemic adverse reactions (60.1% after Dose 1 and 69.7 after Dose 2) have been observed.

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

The most frequent adverse reactions reported following receipt of a booster dose of Nuvaxovid after the two-dose primary series were injection site tenderness (73%), injection site pain (61%), fatigue (53%), muscle pain (52%), headache (46%), malaise (41%), 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.

Nuvaxovid JN.1 (Omicron-adapted Nuvaxovid)

The safety of Nuvaxovid JN.1 is inferred from the safety data of the Nuvaxovid (Original, Wuhan strain) vaccine and the safety data from the adapted Omicron BA.5 vaccine.

A booster dose of the Nuvaxovid monovalent Omicron BA.5 and bivalent Original/Omicron BA.5 vaccines were evaluated in an ongoing Phase 3 study in participants 18 years of age and older (2019nCoV-311 Part 2). In this study, 251 participants received a Nuvaxovid (Original, Wuhan strain) booster dose, 254 received a monovalent Omicron BA.5 booster dose, and 259 participants received a

Nuvaxovid bivalent Original/Omicron BA.5 booster dose. Median follow-up time since the initial booster vaccination was 48 days through the data cutoff date of 31 May 2023.

The overall safety profile for the Nuvaxovid monovalent Omicron BA.5 booster doses was similar to that seen after the Nuvaxovid (Original, Wuhan strain) booster dose. The most frequent adverse reactions were injection site tenderness (> 50%), injection site pain (> 30%), fatigue (> 30%), headache (> 20%), myalgia (> 20%), and malaise (> 10%). No new adverse reactions were identified for the Nuvaxovid monovalent Omicron BA.5 booster doses. In 2019nCoV-311 Part 2 the frequency of local as well as systemic reactogenicity events was greater in women than in men, for all the vaccine constructs that were tested.

Tabulated list of adverse reactions

Unless otherwise stated the frequency categories are based on the safety of Nuvaxovid assessed in 5 clinical trials with a total of 30,070 participants aged 18 years and older who received at least one dose of the two-dose primary series of Nuvaxovid (the median duration of follow-up was 84 days post-Dose 2) and one clinical trial in which 13,354 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).

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		

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)
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] Pain in extremity	Injection site pruritus Chills	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

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V and include batch/Lot number if available.

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 JN.1 is composed of purified full-length SARS-CoV-2 Omicron JN.1 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.

Nuvaxovid JN.1 (Omicron-adapted Nuvaxovid)

The efficacy of Nuvaxovid JN.1 is inferred from the efficacy data of the Nuvaxovid (Original, Wuhan strain) vaccine and immunogenicity data from the adapted vaccine of the Omicron BA.5 strain.

In study 2019nCoV-311 Part 2, a total of 694 participants 18 years of age and older, who were evaluated for immunogenicity and previously received 3 or more doses of the Pfizer-BioNTech COVID-19 vaccine or the Moderna COVID-19 vaccine received 1 of the following as a booster dose: Nuvaxovid (Original, Wuhan strain), Nuvaxovid monovalent Omicron BA.5 vaccine or Nuvaxovid bivalent Original/Omicron BA.5 vaccine. The booster doses were administered a median of 11 – 13 months after the last vaccination, respectively. GMRs and seroresponse rates were evaluated at 1 month after vaccination.

The primary objective of the study was to demonstrate superiority with respect to level of pseudovirus neutralizing antibody titer (ID_{50}) and non-inferiority with respect to seroresponse rate of the anti-Omicron BA.5 immune response induced by a dose of the Nuvaxovid bivalent Original/Omicron BA.5 vaccine relative to the response elicited by a dose of Nuvaxovid (Original, Wuhan strain), and to assess non-inferiority with respect to level of ID_{50} for the original SAR-CoV-2 strain for the Nuvaxovid bivalent Original/Omicron BA.5 vaccine compared to Nuvaxovid (Original, Wuhan strain).

Superiority of the anti-Omicron BA.5 ID_{50} for the Nuvaxovid bivalent Original/Omicron BA.5 vaccine relative to Nuvaxovid (Original, Wuhan strain) was demonstrated, as the lower bound of the two-sided 95% confidence interval (CI) for GMR was >1. Non-inferiority of the anti-Original ID_{50} for the Nuvaxovid bivalent Original/Omicron BA.5 vaccine relative to Nuvaxovid (Original, Wuhan strain) was met, as the lower bound of the two-sided 95% CI for GMR was >0.67.
Non-inferiority of the seroresponse rate to the Omicron BA.5 variant for the Nuvaxovid bivalent Original/Omicron BA.5 vaccine relative to Nuvaxovid (Original, Wuhan strain) was met, as the lower limit of the two-sided 95% CI for the difference in percentages of participants with seroresponse was >-5%. For more details see Table 2.

Exploratory immunogenicity analyses included an assessment of the ID_{50} GMT ratio and difference in seroresponse rates for the Nuvaxovid monovalent Omicron BA.5 vaccine compared to Nuvaxovid (Original, Wuhan strain). The GMT ratio following the booster dose with Nuvaxovid monovalent Omicron BA.5 vaccine compared with the booster dose of Nuvaxovid (Original, Wuhan strain) was 2.5 (two-sided 95% CIs: 2.10, 2.94). The difference in seroresponse rates between the booster dose with Nuvaxovid monovalent Omicron BA.5 vaccine and the booster dose with Nuvaxovid (Original, Wuhan strain) was 33.2% (two-sided 95% CIs: 25.4%, 40.7%). While not formally assessed, these responses would have met the three success criteria for the study.

Table 2: Omicron BA.5 and Wuhan pseudovirus neutralising antibody titres (ID_{50}) and seroresponse rates following booster vaccination with Nuvaxovid monovalent BA.5 vaccine, Nuvaxovid (Original, Wuhan strain), and Nuvaxovid bivalent Original/Omicron BA.5 Vaccine – PP pseudovirus neutralization assay subset; Study 2019nCoV-311 Part 2

Parameters	**Participants ≥ 18 Years**					
	Nuvaxovid Monovalent Omicron BA.5	**Nuvaxovid (Original, Wuhan strain)**	**Nuvaxovid Bivalent Original/Omicron BA.5**	**Bivalent vs. Original Fulfillment of hypothesis testing**	**Monovalent Omicron BA.5 vs. Original**	**Monovalent Omicron BA.5 vs. Bivalent**
Omicron BA.5 Pseudovirus neutralisation						
Baseline[1]						
n1	236	227	231			
GMT (ID_{50})	**348.4**	**326.6**	**293.3**			
95% CI[2]	283.9, 427.6	260.0, 410.4	237.3, 362.6			
Day 28						
n1	235	227	231	**GMTR,** LB of 95% CI > 1.0 criterion for superiority		
Adjusted GMT[3]	**1279.1**	**515.1**	**1017.8**	2.0 **YES**	2.5 NT	1.3 NT
95% CI[2]	1119.7, 1461.1	450.4, 589.0	891.0, 1162.6	1.69, 2.33	2.10, 2.94	1.06, 1.50
GMFR referencing Day 0	**4.4**	**1.8**	**3.6**			
95% CI[2]	3.8, 5.1	1.6, 2.0	3.2, 4.2	Difference in SRR[6] LB of 95% CI > -5% criterion for non-inferiority		
SRR ≥ 4-fold increase,[4] n3/n2 (%)	107/235 (**45.5**)	28/227 (**12.3**)	92/231 (**39.8**)	27.5 **YES**	33.2 NT	5.7 NT
95% CI[5]	39.0, 52.1	8.4, 17.3	33.5, 46.5	19.8, 35.0	25.4, 40.7	-3.3, 14.6
Ancestral (Wuhan) Pseudovirus neutralisation						
Baseline[1]						
n1	236	227	230			
GMT (ID_{50})	1355.4	1259.7	1222.1			
95% CI[2]	1141.7, 1609.2	1044.1, 1519.8	1024.5, 1457.9			
Day 28						
n1	236	227	231	**GMTR** LB of 95% CI > 0.67 criterion for non-inferiority		
Adjusted GMT[3]	2010.2	2205.6	2211.1	1.0 **YES**	0.9	0.9
95% CI[2]	1766.6, 2310.1	1926.4, 2525.1	1932.9, 2529.3	0.84, 1.20	0.78, 1.08	0.77, 1.09

GMFR referencing Day 0	1.6	1.9	1.9			
95% CI[2]	1.4, 1.9	1.6, 2.1	1.6, 2.2	Difference in SRR[6]		
SRR ≥ 4-fold increase,[4] n3/n2 (%)	53/236 (22.5)	52/227 (22.9)	54/230 (23.5)	0.6	-0.4	-1.0
95% CI[5]	17.3, 28.3	17.6, 28.9	18.2, 29.5	-7.2, 8.3	-8.1, 7.2	-8.7, 6.6

Abbreviations: CI = confidence interval; GMFR = geometric mean fold rise; GMT = geometric mean titre; GMTR = geometric mean titre ratio; ID_{50} = 50% inhibitory dilution; LB = lower bound; LLOQ = lower limit of quantitation; n1 = number of participants in the assay-specific PP-IMM analysis set within each visit with non-missing data; n2 = number of participants in the assay-specific PP-IMM analysis set with non-missing data at both day 0 and day 28; n3 = number of participants who reported ≥ 4-fold increase with percentages calculated based on n2 as the denominator; NT = not tested; PP-IMM = per-protocol immunogenicity; SRR = seroresponse rate.

1 Baseline was defined as the last non-missing assessment prior to booster vaccination.

2 The 95% CI for GMT and GMFR were calculated based on the t-distribution of the log-transformed values then back transformed to the original scale for presentation.

[3] An ANCOVA with vaccine group and age group (18-54, ≥ 55 years) as fixed effects and baseline value (Day 0) as covariate was performed that included all vaccine groups to estimate the adjusted GMT for all vaccine groups. Each pairwise comparison included the data from two groups only to estimate the adjusted GMTR between the two vaccine groups. The mean difference between vaccine groups and the corresponding CI limits was then exponentiated to obtain the ratio of ID_{50} GMTs and the corresponding 95% CIs.

[4] The SRR was defined as percentage of participants at each post vaccination visit with a titer ≥ 4-fold rise in ID_{50} level from baseline if the baseline value is equal or above LLOQ or ≥ 4-fold times the LLOQ if the baseline value is below the LLOQ and calculated based on n2 as the denominator.

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

[6] 95% CI for the difference in SRR was calculated based on the method of Miettinen and Nurminen.

Nuvaxovid (Original, Wuhan strain)

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 was a 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; had 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 were 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 conditional marketing 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 24,784 participants who received either Nuvaxovid (n = 16,898) or placebo (n = 7,886), received two doses (Dose 1 on day 0; Dose 2 at day 21, median 21 days [IQR 21-23], range 20-60), 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 = 14,908) were 18 to 64 years old and 12% (n = 1,990) 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 16,100 (95%) participants. Comorbidities included: obesity (body mass index (BMI) $\geq$ 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 $\geq$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 3.

Table 3: 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	16,880	18 (0.1)	3.36	7,814	72 (0.9)	39.74	91.53% (83.31, 95.70)[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 91.53% (95% CI: 83.31, 95.70). No cases of severe COVID-19 were reported in the 16,880 Nuvaxovid participants compared with 4 cases of severe COVID-19 reported in the 7,886 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 ≥ 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 two countries (US and Mexico) where the study was conducted. Sequencing data were available for 70 of the 90 endpoint cases (78%). Of these, 54 out of 70 (77%) were identified as Variants of Concern or Variants Being Monitored. The most common Variants of Concern/Variants Being Monitored identified were Alpha with 52/90 cases (58%), Beta (2/90, 2%), Gamma (3/90, 3%), Iota with 9/90 cases (10%), and Epsilon (19/90, 21%).

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 SARS-CoV-2 at the time of randomisation were not included in the primary efficacy analysis.

Enrolment of adolescents completed in June 2021. Participants were followed for up to 24 months after the second dose for assessments of safety, efficacy, and immunogenicity against COVID-19. Following a 60-day 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 COVID-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 4. Non-inferiority 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 non-inferiority criteria were met.

Table 4: **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 was a 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 were 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 13,971 participants who received either Nuvaxovid (n=6,979) or placebo (n=6,992), 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 (Table 5).

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=5,039) were 18 to 64 years old and 28% (n=1,940) were aged 65 to 84; 49% were female; 95% 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.

Vaccine efficacy of Nuvaxovid to prevent the onset of COVID-19 from 7 days after Dose 2 was 87.2% (95% CI: 78.1, 92.5). No cases of severe COVID-19 were reported in the 6,979 Nuvaxovid

participants compared with 6 cases of severe COVID-19 reported in the 6,992 placebo recipients in the PP-EFF analysis set.

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 (Original, Wuhan strain)			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	6,979	15 (0.2)	9.47	6,992	116 (1.7)	73.88	87.2% (78.1, 92.5)[2, 3]
Subgroup analyses of the primary efficacy endpoint							
18 to 64 years of age	5,039	13 (0.3)	18.86	5,042	108 (2.1)	158.12	88.1% (78.8, 93.3)[2]
65 to 84 years of age	1,940	2 (0.1)[2]	7.08	1,950	8 (0.4)[2]	28.33	75.0% (-25.3, 97.4)[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 118 of the 131 endpoint cases (90%). Of these, 80 out of 118 (68%) were identified as the Alpha variant with the other cases classified as non-Alpha.

Licensed seasonal influenza vaccine co-administration sub-study
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=190), median age was 40 years (range: 22 to 70 years); 94% (n=178) were 18 to 64 years old and 6% (n=12) were aged 65 to 84; 43% were female; 86% were White; 14% 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 was a 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 2,769 participants who received either Nuvaxovid (n=1,413) or placebo (n=1,356), 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); 39% were female; 94% were Black/African American; 5% were White; 3% were multiple races, 1% were Asian; and 2% were Hispanic or Latino; and 5.4% were HIV-positive.

A total of 168 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 57 (4.0%) cases for Nuvaxovid versus 111 (8.2%) cases for placebo. The resultant vaccine efficacy of Nuvaxovid was 50.7% (95% CI: 32.8, 63.9).

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 a 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 84.8-fold increase in neutralising antibodies from a GMT of 68.3 pre-booster (Day 189) to a GMT of 5,834.3 post-booster (Day 217) and an approximate 6.8-fold increase from a peak GMT (14 days post-Dose 2) of 855.2.

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 1,169 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 52.2-fold increase in neutralising antibodies was shown from a GMT of 69 pre-booster (Day 201) to a GMT of 3,603 post-booster (Day 236) and an approximate 5.2-fold increase from a peak GMT (14 days post-Dose 2) of 690.

Safety and immunogenicity of COVID-19 vaccines given as booster doses following completion of a primary vaccination series with another authorised COVID-19 vaccine was evaluated in an independent study in the UK.

The independent, multicentre, randomised, controlled, Phase 2 investigator-initiated trial (CoV-BOOST, EudraCT 2021-002175-19) investigated the immunogenicity of a 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 (Original, Wuhan strain) 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 European Medicines Agency 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 and reproductive and developmental toxicity.

Genotoxicity and Carcinogenicity

In vitro genotoxicity studies were conducted with the Matrix-M adjuvant. The adjuvant was shown to be non-genotoxic. Carcinogenicity studies were not performed. Carcinogenicity is not expected.

Reproductive toxicity

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

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

9 months at 2°C to 8°C, protected from light.

Unopened Nuvaxovid JN.1 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 9-month storage at 2°C to 8°C.

Punctured vial

From a microbiological point of view, after the opening, the vaccine should be used immediately. The single dose vial should be discarded after one dose withdrawal and administration, see section 6.6.

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.

6.5 Nature and contents of container

Single dose vial

0.5 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 one dose of 0.5 mL.

Pack size: 1 single dose vial or 10 single dose vials

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.
- Discard the vial and any excess volume after one 0.5 mL dose withdrawal and administration.

Inspect the vial

- Gently swirl the vial before the dose withdrawal. Do not shake.
- Each 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 one dose of 0.5 mL from the single dose vial can be extracted.
- One dose of 0.5 mL 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.

Discard

- Discard the vial and any excess volume after one dose withdrawal and administration.

Disposal

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

7. MARKETING AUTHORISATION HOLDER

Sanofi Winthrop Industrie
82 Avenue Raspail
94250 Gentilly
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1618/007	10 single dose vials (1 dose per vial)
EU/1/21/1618/009	1 single dose vial (1 dose per vial)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 December 2021
Date of latest renewal: 03 October 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

▼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 JN.1 dispersion for injection in pre-filled syringe
COVID-19 Vaccine (recombinant, adjuvanted)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

These are single dose pre-filled syringes.

One pre-filled syringe contains 1 dose of 0.5 mL, see section 6.5.

One dose (0.5 mL) contains 5 micrograms of the SARS-CoV-2 (Omicron JN.1) 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 JN.1 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

Nuvaxovid JN.1 is administered intramuscularly as a single dose (0.5 mL) for individuals 12 years of age and older regardless of previous vaccination status.

For individuals who have previously been vaccinated with a COVID-19 vaccine, Nuvaxovid JN.1 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Immunocompromised individuals
Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations, see section 4.4.

Paediatric population
The safety and efficacy of Nuvaxovid JN.1 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 JN.1 is for intramuscular injection only, preferably into the deltoid muscle of the upper arm.

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

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. An additional dose of the vaccine should not be given to those who have experienced anaphylaxis to a prior 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 JN.1 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 vaccination. As with all vaccines, vaccination with Nuvaxovid JN.1 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 less than 1 mmol potassium (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 (Original, Wuhan strain) 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 JN.1 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/foetal development, parturition, or post-natal development, see section 5.3.

Administration of Nuvaxovid JN.1 in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and foetus.

Breast-feeding

It is unknown whether Nuvaxovid JN.1 is excreted in human milk.

No effects on the breast-fed newborn/infant are anticipated since the systemic exposure of the breast-feeding woman to Nuvaxovid JN.1 is negligible.

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity, see section 5.3.

4.7 Effects on ability to drive and use machines

Nuvaxovid JN.1 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

Nuvaxovid (Original, Wuhan strain)

Summary of the safety profile after primary series

Participants 18 years of age and older
The most frequent adverse reactions after administration of a Nuvaxovid dose within the primary series were injection site tenderness (75%), injection site pain (62%), fatigue (53%), myalgia (51%), headache (50%), malaise (41%), arthralgia (24%), and nausea or vomiting (14%). 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: 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.

Following co-administration with seasonal influenza vaccine, higher frequencies of local adverse reactions at the Nuvaxovid injection site (70.1% after Dose 1 and 85.0% after Dose 2) and systemic adverse reactions (60.1% after Dose 1 and 69.7 after Dose 2) have been observed.

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

The most frequent adverse reactions reported following receipt of a booster dose of Nuvaxovid after the two-dose primary series were injection site tenderness (73%), injection site pain (61%), fatigue (53%), muscle pain (52%), headache (46%), malaise (41%), 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.

Nuvaxovid JN.1 (Omicron-adapted Nuvaxovid)

The safety of Nuvaxovid JN.1 is inferred from the safety data of the Nuvaxovid (Original, Wuhan strain) vaccine and the safety data from the adapted Omicron BA.5 vaccine.

A booster dose of the Nuvaxovid monovalent Omicron BA.5 and bivalent Original/Omicron BA.5 vaccines were evaluated in an ongoing Phase 3 study in participants 18 years of age and older (2019nCoV-311 Part 2). In this study, 251 participants received a Nuvaxovid (Original, Wuhan strain) booster dose, 254 received a monovalent Omicron BA.5 booster dose, and 259 participants received a Nuvaxovid bivalent Original/Omicron BA.5 booster dose. Median follow-up time since the initial booster vaccination was 48 days through the data cutoff date of 31 May 2023.

The overall safety profile for the Nuvaxovid monovalent Omicron BA.5 booster doses was similar to that seen after the Nuvaxovid (Original, Wuhan strain) booster dose. The most frequent adverse

reactions were injection site tenderness (> 50%), injection site pain (> 30%), fatigue (> 30%), headache (> 20%), myalgia (> 20%), and malaise (> 10%). No new adverse reactions were identified for the Nuvaxovid monovalent Omicron BA.5 booster doses. In 2019nCoV-311 Part 2 the frequency of local as well as systemic reactogenicity events was greater in women than in men, for all the vaccine constructs that were tested.

Tabulated list of adverse reactions

Unless otherwise stated the frequency categories are based on the safety of Nuvaxovid assessed in 5 clinical trials with a total of 30,070 participants aged 18 years and older who received at least one dose of the two-dose primary series of Nuvaxovid (the median duration of follow-up was 84 days post-Dose 2) and one clinical trial in which 13,354 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).

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]	Injection site redness[a,c] Injection site swelling[a]	Injection site pruritus Chills	Injection site warmth	

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)
	Fatigue[a] Malaise[a,b]	Pyrexia[e] Pain in extremity			

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

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V and include batch/Lot number if available.

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 JN.1 is composed of purified full-length SARS-CoV-2 Omicron JN.1 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.

Nuvaxovid JN.1 (Omicron-adapted Nuvaxovid)

The efficacy of Nuvaxovid JN.1 is inferred from the efficacy data of the Nuvaxovid (Original, Wuhan strain) vaccine and immunogenicity data from the adapted vaccine of the Omicron BA.5 strain.

In study 2019nCoV-311 Part 2, a total of 694 participants 18 years of age and older, who were evaluated for immunogenicity and previously received 3 or more doses of the Pfizer-BioNTech COVID-19 vaccine or the Moderna COVID-19 vaccine received 1 of the following as a booster dose:

Nuvaxovid (Original, Wuhan strain), Nuvaxovid monovalent Omicron BA.5 vaccine or Nuvaxovid bivalent Original/Omicron BA.5 vaccine. The booster doses were administered a median of 11 – 13 months after the last vaccination, respectively. GMRs and seroresponse rates were evaluated at 1 month after vaccination.

The primary objective of the study was to demonstrate superiority with respect to level of pseudovirus neutralizing antibody titer (ID_{50}) and non-inferiority with respect to seroresponse rate of the anti-Omicron BA.5 immune response induced by a dose of the Nuvaxovid bivalent Original/Omicron BA.5 vaccine relative to the response elicited by a dose of Nuvaxovid (Original, Wuhan strain), and to assess non-inferiority with respect to level of ID_{50} for the original SAR-CoV-2 strain for the Nuvaxovid bivalent Original/Omicron BA.5 vaccine compared to Nuvaxovid (Original, Wuhan strain).

Superiority of the anti-Omicron BA.5 ID_{50} for the Nuvaxovid bivalent Original/Omicron BA.5 vaccine relative to Nuvaxovid (Original, Wuhan strain) was demonstrated, as the lower bound of the two-sided 95% confidence interval (CI) for GMR was >1. Non-inferiority of the anti-Original ID_{50} for the Nuvaxovid bivalent Original/Omicron BA.5 vaccine relative to Nuvaxovid (Original, Wuhan strain) was met, as the lower bound of the two-sided 95% CI for GMR was >0.67.
Non-inferiority of the seroresponse rate to the Omicron BA.5 variant for the Nuvaxovid bivalent Original/Omicron BA.5 vaccine relative to Nuvaxovid (Original, Wuhan strain) was met, as the lower limit of the two-sided 95% CI for the difference in percentages of participants with seroresponse was >-5%. For more details see Table 2.

Exploratory immunogenicity analyses included an assessment of the ID_{50} GMT ratio and difference in seroresponse rates for the Nuvaxovid monovalent Omicron BA.5 vaccine compared to Nuvaxovid (Original, Wuhan strain). The GMT ratio following the booster dose with Nuvaxovid monovalent Omicron BA.5 vaccine compared with the booster dose of Nuvaxovid (Original, Wuhan strain) was 2.5 (two-sided 95% CIs: 2.10, 2.94). The difference in seroresponse rates between the booster dose with Nuvaxovid monovalent Omicron BA.5 vaccine and the booster dose with Nuvaxovid (Original, Wuhan strain) was 33.2% (two-sided 95% CIs: 25.4%, 40.7%). While not formally assessed, these responses would have met the three success criteria for the study.

Table 2: Omicron BA.5 and Wuhan pseudovirus neutralising antibody titres (ID_{50}) and seroresponse rates following booster vaccination with Nuvaxovid monovalent BA.5 vaccine, Nuvaxovid (Original, Wuhan strain), and Nuvaxovid bivalent Original/Omicron BA.5 Vaccine – PP pseudovirus neutralization assay subset; Study 2019nCoV-311 Part 2

Parameters	**Participants ≥ 18 Years**					
	Nuvaxovid Monovalent Omicron BA.5	**Nuvaxovid (Original, Wuhan strain)**	**Nuvaxovid Bivalent Original/Omicron BA.5**	**Bivalent vs. Original Fulfillment of hypothesis testing**	**Monovalent Omicron BA.5 vs. Original**	**Monovalent Omicron BA.5 vs. Bivalent**
Omicron BA.5 Pseudovirus neutralisation						
Baseline[1]						
n1	236	227	231			
GMT (ID_{50})	**348.4**	**326.6**	**293.3**			
95% CI[2]	283.9, 427.6	260.0, 410.4	237.3, 362.6			
Day 28						
n1	235	227	231	**GMTR,** LB of 95% CI > 1.0 criterion for superiority		

Adjusted GMT[3]	**1279.1**	**515.1**	**1017.8**	2.0 **YES**	2.5 NT	1.3 NT
95% CI[2]	1119.7, 1461.1	450.4, 589.0	891.0, 1162.6	1.69, 2.33	2.10, 2.94	1.06, 1.50
GMFR referencing Day 0	**4.4**	**1.8**	**3.6**			
95% CI[2]	3.8, 5.1	1.6, 2.0	3.2, 4.2	Difference in SRR[6] LB of 95% CI > -5% criterion for non-inferiority		
SRR ≥ 4-fold increase,[4] n3/n2 (%)	107/235 (**45.5**)	28/227 (**12.3**)	92/231 (**39.8**)	27.5 **YES**	33.2 NT	5.7 NT
95% CI[5]	39.0, 52.1	8.4, 17.3	33.5, 46.5	19.8, 35.0	25.4, 40.7	-3.3, 14.6
Ancestral (Wuhan) Pseudovirus neutralisation						
Baseline[1]						
n1	236	227	230			
GMT (ID_{50})	1355.4	1259.7	1222.1			
95% CI[2]	1141.7, 1609.2	1044.1, 1519.8	1024.5, 1457.9			
Day 28						
n1	236	227	231	**GMTR** LB of 95% CI > 0.67 criterion for non-inferiority		
Adjusted GMT[3]	2010.2	2205.6	2211.1	1.0 **YES**	0.9	0.9
95% CI[2]	1766.6, 2310.1	1926.4, 2525.1	1932.9, 2529.3	0.84, 1.20	0.78, 1.08	0.77, 1.09
GMFR referencing Day 0	1.6	1.9	1.9			
95% CI[2]	1.4, 1.9	1.6, 2.1	1.6, 2.2	Difference in SRR[6]		
SRR ≥ 4-fold increase,[4] n3/n2 (%)	53/236 (22.5)	52/227 (22.9)	54/230 (23.5)	0.6	-0.4	-1.0
95% CI[5]	17.3, 28.3	17.6, 28.9	18.2, 29.5	-7.2, 8.3	-8.1, 7.2	-8.7, 6.6

Abbreviations: CI = confidence interval; GMFR = geometric mean fold rise; GMT = geometric mean titre; GMTR = geometric mean titre ratio; ID_{50} = 50% inhibitory dilution; LB = lower bound; LLOQ = lower limit of quantitation; n1 = number of participants in the assay-specific PP-IMM analysis set within each visit with non-missing data; n2 = number of participants in the assay-specific PP-IMM analysis set with non-missing data at both day 0 and day 28; n3 = number of participants who reported ≥ 4 fold increase with percentages calculated based on n2 as the denominator; NT = not tested; PP-IMM = per-protocol immunogenicity; SRR = seroresponse rate.

1 Baseline was defined as the last non-missing assessment prior to booster vaccination.

2 The 95% CI for GMT and GMFR were calculated based on the t-distribution of the log-transformed values then back transformed to the original scale for presentation.

3 An ANCOVA with vaccine group and age group (18-54, ≥ 55 years) as fixed effects and baseline value (Day 0) as covariate was performed that included all vaccine groups to estimate the adjusted GMT for all vaccine groups. Each pairwise comparison included the data from two groups only to estimate the adjusted GMTR between the two vaccine groups. The mean difference between vaccine groups and the corresponding CI limits was then exponentiated to obtain the ratio of ID_{50} GMTs and the corresponding 95% CIs.

4 The SRR was defined as percentage of participants at each post vaccination visit with a titer ≥ 4-fold rise in ID_{50} level from baseline if the baseline value is equal or above LLOQ or ≥ 4-fold times the LLOQ if the baseline value is below the LLOQ and calculated based on n2 as the denominator.

5 The 95% CI for SRR was calculated using the Clopper-Pearson method.

6 95% CI for the difference in SRR was calculated based on the method of Miettinen and Nurminen.

Nuvaxovid (Original, Wuhan strain)

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 was a 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; had 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 were 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 conditional marketing 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 24,784 participants who received either Nuvaxovid (n = 16,898) or placebo (n = 7,886), received two doses (Dose 1 on day 0; Dose 2 at day 21, median 21 days [IQR 21-23], range 20-60), 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 = 14,908) were 18 to 64 years old and 12% (n = 1,990) 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 16,100 (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 3.

Table 3: 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	16,880	18 (0.1)	3.36	7,814	72 (0.9)	39.74	91.53% (83.31, 95.70)[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 91.53% (95% CI: 83.31, 95.70). No cases of severe COVID-19 were reported in the 16,880 Nuvaxovid participants compared with 4 cases of severe COVID-19 reported in the 7,886 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 ≥ 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 two countries (US and Mexico) where the study was conducted. Sequencing data were available for 70 of the 90 endpoint cases (78%). Of these, 54 out of 70 (77%) were identified as Variants of Concern or Variants Being Monitored. The most common Variants of Concern/Variants Being Monitored identified were Alpha with 52/90 cases (58%), Beta (2/90, 2%), Gamma (3/90, 3%), Iota with 9/90 cases (10%), and Epsilon (19/90, 21%).

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 SARS-CoV-2 at the time of randomisation were not included in the primary efficacy analysis.

Enrolment of adolescents completed in June 2021. Participants were followed for up to 24 months after the second dose for assessments of safety, efficacy, and immunogenicity against COVID-19. Following a 60-day 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 COVID-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 4. Non-inferiority 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 non-inferiority criteria were met.

Table 4: **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 was a 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 were 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 13,971 participants who received either Nuvaxovid (n=6,979) or placebo (n=6,992), 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 (Table 5).

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=5,039) were 18 to 64 years old and 28% (n=1,940) were aged 65 to 84; 49% were female; 95% 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.

Vaccine efficacy of Nuvaxovid to prevent the onset of COVID-19 from 7 days after Dose 2 was 87.2% (95% CI: 78.1, 92.5). No cases of severe COVID-19 were reported in the 6,979 Nuvaxovid participants compared with 6 cases of severe COVID-19 reported in the 6,992 placebo recipients in the PP-EFF analysis set.

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 (Original, Wuhan strain)			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	6,979	15 (0.2)	9.47	6,992	116 (1.7)	73.88	87.2% (78.1, 92.5)[2,3]
Subgroup analyses of the primary efficacy endpoint							
18 to 64 years of age	5,039	13 (0.3)	18.86	5,042	108 (2.1)	158.12	88.1% (78.8, 93.3)[2]
65 to 84 years of age	1,940	2 (0.1)[2]	7.08	1,950	8 (0.4)[2]	28.33	75.0% (-25.3, 97.4)[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 118 of the 131 endpoint cases (90%). Of these, 80 out of 118 (68%) were identified as the Alpha variant with the other cases classified as non-Alpha.

Licensed seasonal influenza vaccine co-administration sub-study
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=190), median age was 40 years (range: 22 to 70 years); 94% (n=178) were 18 to 64 years old and 6% (n=12) were aged 65 to 84; 43% were female; 86% were White; 14% 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 was a 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 2,769 participants who received either Nuvaxovid (n=1,413) or placebo (n=1,356), 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); 39% were female; 94% were Black/African American; 5% were White; 3% were multiple races, 1% were Asian; and 2% were Hispanic or Latino; and 5.4% were HIV-positive.

A total of 168 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 57 (4.0%) cases for Nuvaxovid versus 111 (8.2%) cases for placebo. The resultant vaccine efficacy of Nuvaxovid was 50.7% (95% CI: 32.8, 63.9).

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 a 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 84.8-fold increase in neutralising antibodies from a GMT of 68.3 pre-booster (Day 189) to a GMT of 5,834.3

post-booster (Day 217) and an approximate 6.8-fold increase from a peak GMT (14 days post-Dose 2) of 855.2.

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 1,169 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 52.2-fold increase in neutralising antibodies was shown from a GMT of 69 pre-booster (Day 201) to a GMT of 3,603 post-booster (Day 236) and an approximate 5.2-fold increase from a peak GMT (14 days post-Dose 2) of 690.

Safety and immunogenicity of COVID-19 vaccines given as booster doses following completion of a primary vaccination series with another authorised COVID-19 vaccine was evaluated in an independent study in the UK.

The independent, multicentre, randomised, controlled, Phase 2 investigator-initiated trial (CoV-BOOST, EudraCT 2021-002175-19) investigated the immunogenicity of a 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 (Original, Wuhan strain) 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 European Medicines Agency 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 and reproductive and developmental toxicity.

Genotoxicity and Carcinogenicity

In vitro genotoxicity studies were conducted with the Matrix-M adjuvant. The adjuvant was shown to be non-genotoxic. Carcinogenicity studies were not performed. Carcinogenicity is not expected.

Reproductive toxicity

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

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

9 months at 2°C to 8°C, protected from light.

The pre-filled syringe should be discarded after administration, see section 6.6.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.

Keep the pre-filled syringes in the outer carton in order to protect from light.

6.5 Nature and contents of container

Pre-filled syringe

0.5 mL of dispersion in a pre-filled syringe (glass Type I) with a plunger stopper and a tip cap, without a needle or co-packed with a separate needle.

Each pre-filled syringe contains one dose of 0.5 mL.

Pack size:
10 pre-filled syringes
1 pre-filled syringe
1 pre-filled syringe with a separate needle

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.
- The pre-filled syringe 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 prefilled syringe from the carton in the refrigerator.
- Each pre-filled syringe is for single use only.

Inspect the pre-filled syringe

- Do not shake the pre-filled syringe.
- Each pre-filled syringe contains a colourless to slightly yellow, clear to mildly opalescent dispersion free from visible particles.
- Visually inspect the contents of the pre-filled syringe for visible particulate matter and/or discolouration prior to administration. Do not administer the vaccine if either are present.
- Do not use the pre-filled syringe if the tip cap has been removed or is missing.
- Do not use the pre-filled syringe if it leaks or there are some visible cracks on it.

Administer the pre-filled syringe

- Pre-filled syringe without a needle
    - Needles are not included in the pre-filled syringe cartons.
    - Use a sterile needle of the appropriate size for intramuscular injection (21-gauge or thinner needles)
- Pre-filled syringe with a separate needle
    - Use a needle included in the pack.

- With tip cap of the pre-filled syringe upright, remove tip cap twisting counter-clockwise until tip cap releases. Remove tip cap in a slow, steady motion. Avoid pulling tip cap while twisting.

- Attach the needle by twisting in a clockwise direction until the needle fits securely on the syringe.

- Uncap the needle when ready for administration.

- Administer the entire dose intramuscularly, preferably in the deltoid muscle of the upper arm.

Discard

- Discard the pre-filled syringe after administration.

Disposal

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

7. MARKETING AUTHORISATION HOLDER

Sanofi Winthrop Industrie
82 Avenue Raspail
94250 Gentilly
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1618/011	10 pre-filled syringes (1 dose per syringe)
EU/1/21/1618/012	1 pre-filled syringe (1 dose per syringe)
EU/1/21/1618/013	1 pre-filled syringe + 1 needle (1 dose per syringe)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 December 2021
Date of latest renewal: 03 October 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

Serum Institute of India Pvt. Ltd.
S. No. 105-110, Manjari BK, Tal -Haveli, Pune-412307, Maharashtra, India

Name and address of the manufacturer responsible for batch release

Novavax CZ a.s.
Líbalova 2348/1, Chodov, 149 00 Praha 4, Czechia

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

- **Official batch release**

In accordance with Article 114 of Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON LABEL - 2 VIALS; 10 VIALS / 10 doses

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each dose contains 5 micrograms of SARS-CoV-2 recombinant spike protein adjuvanted with Matrix- M

3. LIST OF EXCIPIENTS

Adjuvant Matrix-M: Fraction-A and Fraction-C of *Quillaja saponaria* Molina extract

Excipients: disodium hydrogen phosphate heptahydrate, sodium dihydrogen phosphate monohydrate, disodium hydrogen phosphate dihydrate, sodium chloride, polysorbate 80, cholesterol, phosphatidylcholine (including all-rac-α-Tocopherol), potassium dihydrogen phosphate, potassium chloride and water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for injection
10 multidose vials
2 multidose vials
Each vial contains 10 doses of 0.5 mL
5 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use

Read the package leaflet before use.

For more information, scan or visit
www.NovavaxCovidVaccine.com

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
After first puncture, store at 2ºC to 8ºC, use within 12 hours or within 6 hours at room temperature (maximum 25°C).
Store in the original carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi Winthrop Industrie
82 Avenue Raspail, 94250 Gentilly, France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1618/001
EU/1/21/1618/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL - MULTIDOSE VIAL (10 DOSES)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

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

2. METHOD OF ADMINISTRATION

IM

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 doses of 0.5 mL
5 mL

6. OTHER

Date:
Time:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON LABEL – 2 VIALS; 10 VIALS / 5 doses

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each dose contains 5 micrograms of SARS-CoV-2 recombinant spike protein adjuvanted with Matrix- M

3. LIST OF EXCIPIENTS

Adjuvant Matrix-M: Fraction-A and Fraction-C of *Quillaja saponaria* Molina extract

Excipients: disodium hydrogen phosphate heptahydrate, sodium dihydrogen phosphate monohydrate, disodium hydrogen phosphate dihydrate, sodium chloride, polysorbate 80, cholesterol, phosphatidylcholine (including all-rac-α-Tocopherol), potassium dihydrogen phosphate, potassium chloride and water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for injection
10 multidose vials
2 multidose vials
Each vial contains 5 doses of 0.5 mL
2.5 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use

Read the package leaflet before use.

For more information, scan or visit
www.NovavaxCovidVaccine.com

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
After first puncture, store at 2ºC to 8ºC, use within 12 hours or within 6 hours at room temperature (maximum 25°C).
Store in the original carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi Winthrop Industrie
82 Avenue Raspail, 94250 Gentilly, France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1618/002
EU/1/21/1618/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL – MULTIDOSE VIAL (5 DOSES)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

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

2. METHOD OF ADMINISTRATION

IM

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 doses of 0.5 mL
2.5 mL

6. OTHER

Date:
Time:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON LABEL – 2 VIALS; 10 VIALS / 5 doses

1. NAME OF THE MEDICINAL PRODUCT

Nuvaxovid XBB.1.5 dispersion for injection
COVID-19 Vaccine (recombinant, adjuvanted)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each dose contains 5 micrograms of SARS-CoV-2 (Omicron XBB.1.5) recombinant spike protein adjuvanted with Matrix-M

3. LIST OF EXCIPIENTS

Adjuvant Matrix-M: Fraction-A and Fraction-C of *Quillaja saponaria* Molina extract

Excipients: disodium hydrogen phosphate heptahydrate, sodium dihydrogen phosphate monohydrate, disodium hydrogen phosphate dihydrate, sodium chloride, polysorbate 80, cholesterol, phosphatidylcholine (including all-rac-α-Tocopherol), potassium dihydrogen phosphate, potassium chloride and water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for injection
10 multidose vials
2 multidose vials
Each vial contains 5 doses of 0.5 mL
2.5 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use

Read the package leaflet before use.

For more information, scan or visit
www.NovavaxCovidVaccine.com

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
After first puncture, store at 2ºC to 8ºC, use within 12 hours or within 6 hours at room temperature (maximum 25°C).
Store in the original carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi Winthrop Industrie
82 Avenue Raspail, 94250 Gentilly, France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1618/006
EU/1/21/1618/008

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL – MULTIDOSE VIAL (5 DOSES)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Nuvaxovid XBB.1.5 dispersion for injection
COVID-19 Vaccine (recombinant, adjuvanted)

2. METHOD OF ADMINISTRATION

IM

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 doses of 0.5 mL
2.5 mL

6. OTHER

Date:
Time:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON LABEL – 1 VIAL 10 VIALS / 1 dose

1. NAME OF THE MEDICINAL PRODUCT

Nuvaxovid XBB.1.5 dispersion for injection
COVID-19 Vaccine (recombinant, adjuvanted)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each dose contains 5 micrograms of SARS-CoV-2 (Omicron XBB.1.5) recombinant spike protein adjuvanted with Matrix-M

3. LIST OF EXCIPIENTS

Adjuvant Matrix-M: Fraction-A and Fraction-C of *Quillaja saponaria* Molina extract

Excipients: disodium hydrogen phosphate heptahydrate, sodium dihydrogen phosphate monohydrate, disodium hydrogen phosphate dihydrate, sodium chloride, polysorbate 80, cholesterol, phosphatidylcholine (including all-rac-α-Tocopherol), potassium dihydrogen phosphate, potassium chloride and water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for injection
10 single dose vials
One single dose vial
Each vial contains 1 dose of 0.5 mL
0.5 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use

Read the package leaflet before use.

For more information, scan or visit
www.NovavaxCovidVaccine.com

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Discard vial and any excess volume after one dose withdrawal and administration.
Store in the original carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi Winthrop Industrie
82 Avenue Raspail, 94250 Gentilly, France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1618/005
EU/1/21/1618/010

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL – SINGLE DOSE VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Nuvaxovid XBB.1.5 dispersion for injection
COVID-19 Vaccine (recombinant, adjuvanted)

2. METHOD OF ADMINISTRATION

IM

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose of 0.5 mL
0.5 mL

6. OTHER

Open here

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON LABEL - 1 VIAL 10 VIALS / 1 dose

1. NAME OF THE MEDICINAL PRODUCT

Nuvaxovid JN.1 dispersion for injection
COVID-19 Vaccine (recombinant, adjuvanted)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each dose contains 5 micrograms of SARS-CoV-2 (Omicron JN.1) recombinant spike protein adjuvanted with Matrix-M

3. LIST OF EXCIPIENTS

Adjuvant Matrix-M: Fraction-A and Fraction-C of *Quillaja saponaria* Molina extract

Excipients: disodium hydrogen phosphate heptahydrate, sodium dihydrogen phosphate monohydrate, disodium hydrogen phosphate dihydrate, sodium chloride, polysorbate 80, cholesterol, phosphatidylcholine (including all-rac-α-Tocopherol), potassium dihydrogen phosphate, potassium chloride and water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for injection
10 single dose vials
One single dose vial
Each vial contains 1 dose of 0.5 mL
0.5 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use

Read the package leaflet before use.

For more information, scan or visit
www.NovavaxCovidVaccine.com

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Discard vial and any excess volume after one dose withdrawal and administration.
Store in the original carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi Winthrop Industrie
82 Avenue Raspail, 94250 Gentilly, France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1618/007
EU/1/21/1618/009

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL - SINGLE DOSE VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Nuvaxovid JN.1 dispersion for injection
COVID-19 Vaccine (recombinant, adjuvanted)

2. METHOD OF ADMINISTRATION

IM

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose of 0.5 mL
0.5 mL

6. OTHER

Open here

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON LABEL - 1 PRE-FILLED SYRINGE ; 10 PRE-FILLED SYRINGES / 1 dose

1. NAME OF THE MEDICINAL PRODUCT

Nuvaxovid JN.1 dispersion for injection in pre-filled syringe
COVID-19 Vaccine (recombinant, adjuvanted)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each dose contains 5 micrograms of SARS-CoV-2 (Omicron JN.1) recombinant spike protein adjuvanted with Matrix-M

3. LIST OF EXCIPIENTS

Adjuvant Matrix-M: Fraction-A and Fraction-C of *Quillaja saponaria* Molina extract

Excipients: disodium hydrogen phosphate heptahydrate, sodium dihydrogen phosphate monohydrate, disodium hydrogen phosphate dihydrate, sodium chloride, polysorbate 80, cholesterol, phosphatidylcholine (including all-rac-α-Tocopherol), potassium dihydrogen phosphate, potassium chloride and water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for injection
10 pre-filled syringes
1 pre-filled syringe
1 pre-filled syringe with needle
Each pre-filled syringe contains 1 dose of 0.5 mL
0.5 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use

Read the package leaflet before use.

For more information, scan or visit
www.NovavaxCovidVaccine.com

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Discard the pre-filled syringe after administration.
Store in the original carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi Winthrop Industrie
82 Avenue Raspail, 94250 Gentilly, France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1618/011
EU/1/21/1618/012
EU/1/21/1618/013

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL - PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Nuvaxovid JN.1 dispersion for injection
COVID-19 Vaccine (recombinant, adjuvanted)

2. METHOD OF ADMINISTRATION

IM

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose of 0.5 mL
0.5 mL

6. OTHER

Open here

B. PACKAGE LEAFLET

Package leaflet: Information for the user

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

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you receive this vaccine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Nuvaxovid is and what it is used for
2. What you need to know before you receive Nuvaxovid
3. How Nuvaxovid is given
4. Possible side effects
5. How to store Nuvaxovid
6. Contents of the pack and other information

1. What Nuvaxovid is and what it is used for

Nuvaxovid is a vaccine used to prevent COVID-19 caused by the SARS-CoV-2 virus.

Nuvaxovid is given to individuals 12 years of age and older.

The vaccine causes the immune system (the body's natural defences) to produce antibodies and specialised white blood cells that work against the virus, to give protection against COVID-19. None of the ingredients in this vaccine can cause COVID-19.

2. What you need to know before you receive Nuvaxovid

Nuvaxovid should not be given
- if you are allergic to the active substance or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor, pharmacist, or nurse before you are given Nuvaxovid if:
- you have ever had a severe or life-threatening allergic reaction after receiving any other vaccine injection or after you were given Nuvaxovid in the past,
- you have ever fainted following any needle injection,
- you have a high fever (over 38°C) or severe infection. However, you can have your vaccination if you have a mild fever or upper airway infection like a cold,
- you have bleeding problems, you bruise easily or you use a medicine to prevent blood clots,
- your immune system does not work properly (immunodeficiency) or you are taking medicines that weaken the immune system (such as high-dose corticosteroids, immunosuppressants, or cancer medicines).

There is an increased risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) after vaccination with Nuvaxovid, see section 4. These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days.
Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist, or nurse before you are given Nuvaxovid.

As with any vaccine, the 2-dose vaccination course of Nuvaxovid may not fully protect all those who receive it and it is not known how long you will be protected.

Children

Nuvaxovid is not recommended for children aged below 12 years. Currently, there is no information available on the use of Nuvaxovid in children younger than 12 years of age.

Other medicines and Nuvaxovid

Tell your doctor, pharmacist, or nurse if you are taking, have recently taken, or might take any other medicines or vaccines.

Pregnancy and breastfeeding

If you are pregnant or breastfeeding, think you may be pregnant, or are planning to have a baby, ask your doctor, pharmacist, or nurse for advice before you receive this vaccine.

Driving and using machines

Some of the side effects of Nuvaxovid listed in section 4 (Possible side effects) may temporarily reduce your ability to drive and use machines (for example, feeling faint or lightheaded or feeling very tired).

Do not drive or use machines if you are feeling unwell after vaccination. Wait until any effects of the vaccine have worn off before you drive or use machines.

Nuvaxovid contains sodium and potassium

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

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

3. How Nuvaxovid is given

Individuals 12 years of age and older
Nuvaxovid will be given to you as two separate 0.5 mL injections.

Your doctor, pharmacist, or nurse will inject the vaccine into a muscle, usually in your upper arm.

It is recommended that you receive the second dose of Nuvaxovid 3 weeks after your first dose to receive the full course of this vaccine.

A booster dose of Nuvaxovid may be given approximately 3 months after the second dose in individuals 12 years of age and older.

During and after each injection of the vaccine, your doctor, pharmacist, or nurse will watch over you for around 15 minutes to monitor for signs of an allergic reaction.

If you miss an appointment for your second injection of Nuvaxovid ask your doctor or nurse for advice. If you miss a scheduled injection, you may not be fully protected against COVID-19.

4. Possible side effects

Like all medicines, this vaccine can cause side effects, although not everybody gets them. Most side effects go away within a few days of appearing. If symptoms persist, contact your doctor, pharmacist or nurse.

As with other vaccines, you may feel pain or discomfort at the injection site, or you may see some redness and swelling at this site. However, these reactions usually clear up within a few days.

Get **urgent** medical attention if you get any of the following signs and symptoms of an allergic reaction:

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

Talk to your doctor or nurse if you develop any other side effects. These can include:

Very common (may affect more than 1 in 10 people):

- headache
- feeling sick (nausea) or getting sick (vomiting)
- muscle ache
- joint pain
- tenderness or pain where the injection is given
- feeling very tired (fatigue)
- generally feeling unwell

Common (may affect up to 1 in 10 people):

- redness where the injection is given
- swelling where the injection is given
- fever (>38°C)
- pain or discomfort in the arm, hand, leg and/or foot (pain in the extremity)

Uncommon (may affect up to 1 in 100 people):

- enlarged lymph nodes
- high blood pressure
- itchy skin, rash or hives
- redness of the skin
- itchy skin where the injection is given
- chills

Rare (may affect up to 1 in 1000 people):
- warmth where the injection is given

Not known (cannot be estimated from available data):
- severe allergic reaction
- unusual feeling in the skin, such as tingling or a crawling feeling (paraesthesia)
- decreased feeling or sensitivity, especially in the skin (hypoaesthesia)
- inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis), which can result in breathlessness, palpitations or chest pain

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V and include batch/Lot number if available. By reporting side effects, you can help provide more information on the safety of this vaccine.

5. How to store Nuvaxovid

Keep this medicine out of the sight and reach of children.

Your doctor, pharmacist, or nurse is responsible for storing this vaccine and disposing of any unused product correctly.

Information about storage, expiry, use and handling are described in the section intended for healthcare professionals at the end of the package leaflet.

6. Contents of the pack and other information

What Nuvaxovid contains

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

  *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.

- Matrix-M is included in this vaccine as an adjuvant. Adjuvants are substances included in certain vaccines to accelerate, improve, and/or prolong the protective effects of the vaccine. Matrix-M adjuvant contains Fraction-A (42.5 micrograms) and Fraction-C (7.5 micrograms) of *Quillaja saponaria* Molina extract per 0.5 mL dose.

- The other ingredients (excipients) included in Nuvaxovid are:
  - Disodium hydrogen phosphate heptahydrate
  - Sodium dihydrogen phosphate monohydrate
  - Disodium hydrogen phosphate dihydrate
  - Sodium chloride
  - Polysorbate 80
  - Cholesterol
  - Phosphatidylcholine (including all-rac-α-Tocopherol)
  - Potassium dihydrogen phosphate
  - Potassium chloride
  - Sodium hydroxide (for the adjustment of pH)
  - Hydrochloric acid (for the adjustment of pH)

- Water for injections

What Nuvaxovid looks like and contents of the pack

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

5-dose vial
- 2.5 mL of dispersion for injection in a vial with a rubber stopper and a blue flip-off top.
- Pack size: 2 multidose vials or 10 multidose vials. Each vial contains 5 doses of 0.5 mL.

10-dose vial
- 5 mL of dispersion for injection in a vial with a rubber stopper and a blue flip-off top.
- Pack size: 2 multidose vials or 10 multidose vials. Each vial contains 10 doses of 0.5 mL.

Not all pack sizes may be marketed.

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This leaflet was last revised in.

Scan the code with a mobile device to get the package leaflet in different languages.

Or visit the URL: https://www.NovavaxCovidVaccine.com

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

The following information is intended for healthcare professionals only:

Administer Nuvaxovid intramuscularly, preferably into the deltoid muscle of the upper arm, as two doses, 3 weeks apart.

A booster dose of Nuvaxovid may be given approximately 3 months after the second dose in individuals 12 years of age and older.

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.

Handling instructions and administration

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

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 in a refrigerator (2°C – 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 at 2°C to 8°C or 6 hours at room temperature (maximum 25°C) 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.
- 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 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.
    - 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.

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.

Disposal

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

Package leaflet: Information for the user

Nuvaxovid XBB.1.5 dispersion for injection
COVID-19 Vaccine (recombinant, adjuvanted)

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you receive this vaccine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Nuvaxovid XBB.1.5 is and what it is used for
2. What you need to know before you receive Nuvaxovid XBB.1.5
3. How Nuvaxovid XBB.1.5 is given
4. Possible side effects
5. How to store Nuvaxovid XBB.1.5
6. Contents of the pack and other information

1. What Nuvaxovid XBB.1.5 is and what it is used for

Nuvaxovid XBB.1.5 is a vaccine used to prevent COVID-19 caused by the SARS-CoV-2 virus.

Nuvaxovid XBB.1.5 is given to individuals 12 years of age and older.

The vaccine causes the immune system (the body's natural defences) to produce antibodies and specialised white blood cells that work against the virus, to give protection against COVID-19. None of the ingredients in this vaccine can cause COVID-19.

2. What you need to know before you receive Nuvaxovid XBB.1.5

Nuvaxovid XBB.1.5 should not be given
- if you are allergic to the active substance or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor, pharmacist, or nurse before you are given Nuvaxovid XBB.1.5 if:
- you have ever had a severe or life-threatening allergic reaction after receiving any other vaccine injection or after you were given Nuvaxovid or Nuvaxovid XBB.1.5 in the past,
- you have ever fainted following any needle injection,
- you have a high fever (over 38°C) or severe infection. However, you can have your vaccination if you have a mild fever or upper airway infection like a cold,
- you have bleeding problems, you bruise easily or you use a medicine to prevent blood clots,
- your immune system does not work properly (immunodeficiency) or you are taking medicines that weaken the immune system (such as high-dose corticosteroids, immunosuppressants, or cancer medicines).

There is an increased risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) after vaccination with Nuvaxovid, see section 4. These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days.
Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist, or nurse before you are given Nuvaxovid XBB.1.5.

As with any vaccine, a single dose of Nuvaxovid XBB.1.5 may not fully protect all those who receive it and it is not known how long you will be protected.

Children

Nuvaxovid XBB.1.5 is not recommended for children aged below 12 years. Currently, there is no information available on the use of Nuvaxovid XBB.1.5 in children younger than 12 years of age.

Other medicines and Nuvaxovid XBB.1.5

Tell your doctor, pharmacist, or nurse if you are taking, have recently taken, or might take any other medicines or vaccines.

Pregnancy and breastfeeding

If you are pregnant or breastfeeding, think you may be pregnant, or are planning to have a baby, ask your doctor, pharmacist, or nurse for advice before you receive this vaccine.

Driving and using machines

Some of the side effects of Nuvaxovid XBB.1.5 listed in section 4 (Possible side effects) may temporarily reduce your ability to drive and use machines (for example, feeling faint or lightheaded or feeling very tired).

Do not drive or use machines if you are feeling unwell after vaccination. Wait until any effects of the vaccine have worn off before you drive or use machines.

Nuvaxovid XBB.1.5 contains sodium and potassium

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

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

3. How Nuvaxovid XBB.1.5 is given

Individuals 12 years of age and older
Nuvaxovid XBB.1.5 will be given to you as a single dose 0.5 mL injection.

If you were previously vaccinated with a COVID-19 vaccine, Nuvaxovid XBB.1.5 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Your doctor, pharmacist, or nurse will inject the vaccine into a muscle, usually in your upper arm.

During and after each injection of the vaccine, your doctor, pharmacist, or nurse will watch over you for around 15 minutes to monitor for signs of an allergic reaction.

Additional doses (0.5 mL) of Nuvaxovid XBB.1.5 may be administered at the discretion of your physician, taking into consideration your clinical conditions in line with national recommendations.

Immunocompromised individuals
If your immune system does not work properly additional doses may be administered in line with national recommendations.

4. Possible side effects

Like all medicines, this vaccine can cause side effects, although not everybody gets them. Most side effects go away within a few days of appearing. If symptoms persist, contact your doctor, pharmacist or nurse.

As with other vaccines, you may feel pain or discomfort at the injection site, or you may see some redness and swelling at this site. However, these reactions usually clear up within a few days.

Get **urgent** medical attention if you get any of the following signs and symptoms of an allergic reaction:
- feeling faint or light-headed
- changes in your heartbeat
- shortness of breath
- wheezing
- swelling of your lips, face, or throat
- hives or rash
- nausea or vomiting
- stomach pain

Talk to your doctor or nurse if you develop any other side effects. These can include:

Very common (may affect more than 1 in 10 people):
- headache
- feeling sick (nausea) or getting sick (vomiting)
- muscle ache
- joint pain
- tenderness or pain where the injection is given
- feeling very tired (fatigue)
- generally feeling unwell

Common (may affect up to 1 in 10 people):
- redness where the injection is given
- swelling where the injection is given
- fever (>38°C)
- pain or discomfort in the arm, hand, leg and/or foot (pain in the extremity)

Uncommon (may affect up to 1 in 100 people):
- enlarged lymph nodes
- high blood pressure
- itchy skin, rash or hives
- redness of the skin
- itchy skin where the injection is given
- chills

Rare (may affect up to 1 in 1000 people):
- warmth where the injection is given

Not known (cannot be estimated from available data):
- severe allergic reaction
- unusual feeling in the skin, such as tingling or a crawling feeling (paraesthesia)
- decreased feeling or sensitivity, especially in the skin (hypoaesthesia)
- inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis), which can result in breathlessness, palpitations or chest pain

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V and include batch/Lot number if available. By reporting side effects, you can help provide more information on the safety of this vaccine.

5. How to store Nuvaxovid XBB.1.5

Keep this medicine out of the sight and reach of children.

Your doctor, pharmacist, or nurse is responsible for storing this vaccine and disposing of any unused product correctly.

Information about storage, expiry, use and handling are described in the section intended for healthcare professionals at the end of the package leaflet.

6. Contents of the pack and other information

What Nuvaxovid XBB.1.5 contains

- One dose (0.5 mL) Nuvaxovid XBB.1.5 contains 5 micrograms of SARS-CoV-2 (Omicron XBB.1.5) spike protein* and is adjuvanted with Matrix-M.

  *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.

- Matrix-M is included in this vaccine as an adjuvant. Adjuvants are substances included in certain vaccines to accelerate, improve, and/or prolong the protective effects of the vaccine. Matrix-M adjuvant contains Fraction-A (42.5 micrograms) and Fraction-C (7.5 micrograms) of *Quillaja saponaria* Molina extract per 0.5 mL dose.

- The other ingredients (excipients) included in Nuvaxovid XBB.1.5 are:
  - Disodium hydrogen phosphate heptahydrate
  - Sodium dihydrogen phosphate monohydrate
  - Disodium hydrogen phosphate dihydrate
  - Sodium chloride
  - Polysorbate 80
  - Cholesterol
  - Phosphatidylcholine (including all-rac-α-Tocopherol)
  - Potassium dihydrogen phosphate
  - Potassium chloride
  - Sodium hydroxide (for the adjustment of pH)

- Hydrochloric acid (for the adjustment of pH)
- Water for injections

What Nuvaxovid XBB.1.5 looks like and contents of the pack

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

Single dose vial of 1 dose
- 0.5 mL of dispersion for injection in a vial with a rubber stopper and a blue flip-off top.
- Pack size: 1 single dose vial or 10 single dose vials. Each vial contains 1 dose of 0.5 mL.

Multidose vial of 5-doses
- 2.5 mL of dispersion for injection in a vial with a rubber stopper and a blue flip-off top.
- Pack size: 2 multidose vials or 10 multidose vials. Each vial contains 5 doses of 0.5 mL.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
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Manufacturer
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This leaflet was last revised in.

Scan the code with a mobile device to get the package leaflet in different languages.

Or visit the URL: https://www.NovavaxCovidVaccine.com

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

The following information is intended for healthcare professionals only:

Administer Nuvaxovid XBB.1.5 intramuscularly, preferably into the deltoid muscle of the upper arm, as a single dose.

For individuals who have previously been vaccinated with a COVID-19 vaccine, Nuvaxovid XBB.1.5 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

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

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.

Handling instructions and administration

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

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 in a refrigerator (2°C – 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.
- Single dose vial
    - Discard the vial and any excess volume after one dose withdrawal and administration.
- Multidose vial
    - Use within 12 hours at 2°C to 8°C or 6 hours at room temperature (maximum 25°C) after first needle puncture. Record the date and time of discard on the vial label.

Inspect the vial

- Gently swirl the vial before the dose withdrawal. Do not shake. Gently swirl the multidose vial before each additional dose withdrawal.
- Each vial contains a colourless to slightly yellow, clear to mildly opalescent dispersion.
- 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 one dose of 0.5 mL from the single dose vial or a maximum of 5 doses of 0.5 mL from the multidose vial (vial of 2.5 mL) 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 of multidose vial

- Store the opened multidose 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.

Discard

- Single dose vial
    - Discard the vial and any excess volume after one dose withdrawal and administration.
- Multidose vial
    - 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 needle puncture of the vial.

Disposal

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

Package leaflet: Information for the user

Nuvaxovid JN.1 dispersion for injection
COVID-19 Vaccine (recombinant, adjuvanted)

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you receive this vaccine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Nuvaxovid JN.1 is and what it is used for
2. What you need to know before you receive Nuvaxovid JN.1
3. How Nuvaxovid JN.1 is given
4. Possible side effects
5. How to store Nuvaxovid JN.1
6. Contents of the pack and other information

1. What Nuvaxovid JN.1 is and what it is used for

Nuvaxovid JN.1 is a vaccine used to prevent COVID-19 caused by the SARS-CoV-2 virus.

Nuvaxovid JN.1 is given to individuals 12 years of age and older.

The vaccine causes the immune system (the body's natural defences) to produce antibodies and specialised white blood cells that work against the virus, to give protection against COVID-19. None of the ingredients in this vaccine can cause COVID-19.

2. What you need to know before you receive Nuvaxovid JN.1

Nuvaxovid JN.1 should not be given
- if you are allergic to the active substance or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor, pharmacist, or nurse before you are given Nuvaxovid JN.1 if:
- you have ever had a severe or life-threatening allergic reaction after receiving any other vaccine injection or after you were given Nuvaxovid or Nuvaxovid JN.1 in the past,
- you have ever fainted following any needle injection,
- you have a high fever (over 38°C) or severe infection. However, you can have your vaccination if you have a mild fever or upper airway infection like a cold,
- you have bleeding problems, you bruise easily or you use a medicine to prevent blood clots,
- your immune system does not work properly (immunodeficiency) or you are taking medicines that weaken the immune system (such as high-dose corticosteroids, immunosuppressants, or cancer medicines).

There is an increased risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) after vaccination with Nuvaxovid, see section 4. These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days.
Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist, or nurse before you are given Nuvaxovid JN.1.

As with any vaccine, a single dose of Nuvaxovid JN.1 may not fully protect all those who receive it and it is not known how long you will be protected.

Children

Nuvaxovid JN.1 is not recommended for children aged below 12 years. Currently, there is no information available on the use of Nuvaxovid JN.1 in children younger than 12 years of age.

Other medicines and Nuvaxovid JN.1

Tell your doctor, pharmacist, or nurse if you are taking, have recently taken, or might take any other medicines or vaccines.

Pregnancy and breastfeeding

If you are pregnant or breastfeeding, think you may be pregnant, or are planning to have a baby, ask your doctor, pharmacist, or nurse for advice before you receive this vaccine.

Driving and using machines

Some of the side effects of Nuvaxovid JN.1 listed in section 4 (Possible side effects) may temporarily reduce your ability to drive and use machines (for example, feeling faint or lightheaded or feeling very tired).

Do not drive or use machines if you are feeling unwell after vaccination. Wait until any effects of the vaccine have worn off before you drive or use machines.

Nuvaxovid JN.1 contains sodium and potassium

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

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

3. How Nuvaxovid JN.1 is given

Individuals 12 years of age and older
Nuvaxovid JN.1 will be given to you as a single dose 0.5 mL injection.

If you were previously vaccinated with a COVID-19 vaccine, Nuvaxovid JN.1 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Your doctor, pharmacist, or nurse will inject the vaccine into a muscle, usually in your upper arm.

During and after each injection of the vaccine, your doctor, pharmacist, or nurse will watch over you for around 15 minutes to monitor for signs of an allergic reaction.

Additional doses (0.5 mL) of Nuvaxovid JN.1 may be administered at the discretion of your physician, taking into consideration your clinical conditions in line with national recommendations.

Immunocompromised individuals
If your immune system does not work properly additional doses may be administered in line with national recommendations.

4. Possible side effects

Like all medicines, this vaccine can cause side effects, although not everybody gets them. Most side effects go away within a few days of appearing. If symptoms persist, contact your doctor, pharmacist or nurse.

As with other vaccines, you may feel pain or discomfort at the injection site, or you may see some redness and swelling at this site. However, these reactions usually clear up within a few days.

Get **urgent** medical attention if you get any of the following signs and symptoms of an allergic reaction:
- feeling faint or light-headed
- changes in your heartbeat
- shortness of breath
- wheezing
- swelling of your lips, face, or throat
- hives or rash
- nausea or vomiting
- stomach pain

Talk to your doctor or nurse if you develop any other side effects. These can include:

Very common (may affect more than 1 in 10 people):
- headache
- feeling sick (nausea) or getting sick (vomiting)
- muscle ache
- joint pain
- tenderness or pain where the injection is given
- feeling very tired (fatigue)
- generally feeling unwell

Common (may affect up to 1 in 10 people):
- redness where the injection is given
- swelling where the injection is given
- fever (>38°C)
- pain or discomfort in the arm, hand, leg and/or foot (pain in the extremity)

Uncommon (may affect up to 1 in 100 people):
- enlarged lymph nodes
- high blood pressure
- itchy skin, rash or hives
- redness of the skin
- itchy skin where the injection is given
- chills

Rare (may affect up to 1 in 1000 people):
- warmth where the injection is given

Not known (cannot be estimated from available data):
- severe allergic reaction
- unusual feeling in the skin, such as tingling or a crawling feeling (paraesthesia)
- decreased feeling or sensitivity, especially in the skin (hypoaesthesia)
- inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis), which can result in breathlessness, palpitations or chest pain

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V and include batch/Lot number if available. By reporting side effects, you can help provide more information on the safety of this vaccine.

5. How to store Nuvaxovid JN.1

Keep this medicine out of the sight and reach of children.

Your doctor, pharmacist, or nurse is responsible for storing this vaccine and disposing of any unused product correctly.

Information about storage, expiry, use and handling are described in the section intended for healthcare professionals at the end of the package leaflet.

6. Contents of the pack and other information

What Nuvaxovid JN.1 contains

- One dose (0.5 mL) Nuvaxovid JN.1 contains 5 micrograms of SARS-CoV-2 (Omicron JN.1) spike protein* and is adjuvanted with Matrix-M.

  *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.

- Matrix-M is included in this vaccine as an adjuvant. Adjuvants are substances included in certain vaccines to accelerate, improve, and/or prolong the protective effects of the vaccine. Matrix-M adjuvant contains Fraction-A (42.5 micrograms) and Fraction-C (7.5 micrograms) of *Quillaja saponaria* Molina extract per 0.5 mL dose.

- The other ingredients (excipients) included in Nuvaxovid JN.1 are:
  - Disodium hydrogen phosphate heptahydrate
  - Sodium dihydrogen phosphate monohydrate
  - Disodium hydrogen phosphate dihydrate
  - Sodium chloride
  - Polysorbate 80
  - Cholesterol
  - Phosphatidylcholine (including all-rac-α-Tocopherol)
  - Potassium dihydrogen phosphate
  - Potassium chloride
  - Sodium hydroxide (for the adjustment of pH)

- Hydrochloric acid (for the adjustment of pH)
- Water for injections

What Nuvaxovid JN.1 looks like and contents of the pack

- The dispersion is colourless to slightly yellow, clear to mildly opalescent (pH 7.2).
- 0.5 mL of dispersion for injection in a vial with a rubber stopper and a blue flip-off top.
- Pack size: 1 single dose vial or 10 single dose vials. Each vial contains 1 dose of 0.5 mL.

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This leaflet was last revised in.

Scan the code with a mobile device to get the package leaflet in different languages.

Or visit the URL: https://www.NovavaxCovidVaccine.com

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

The following information is intended for healthcare professionals only:

Administer Nuvaxovid JN.1 intramuscularly, preferably into the deltoid muscle of the upper arm, as a single dose.

For individuals who have previously been vaccinated with a COVID-19 vaccine, Nuvaxovid JN.1 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

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

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.

Handling instructions and administration

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

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 in a refrigerator (2°C – 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.
- Discard the vial and any excess volume after one dose withdrawal and administration.

Inspect the vial

- Gently swirl the vial before the dose withdrawal. Do not shake.
- Each vial contains a colourless to slightly yellow, clear to mildly opalescent dispersion.
- 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 one dose of 0.5 mL from the single dose vial can be extracted.
- One dose of 0.5 mL 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.

Discard

- Discard the vial and any excess volume after one dose withdrawal and administration.

Disposal

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

Package leaflet: Information for the user

Nuvaxovid JN.1 dispersion for injection in pre-filled syringe
COVID-19 Vaccine (recombinant, adjuvanted)

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you receive this vaccine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Nuvaxovid JN.1 is and what it is used for
2. What you need to know before you receive Nuvaxovid JN.1
3. How Nuvaxovid JN.1 is given
4. Possible side effects
5. How to store Nuvaxovid JN.1
6. Contents of the pack and other information

1. What Nuvaxovid JN.1 is and what it is used for

Nuvaxovid JN.1 is a vaccine used to prevent COVID-19 caused by the SARS-CoV-2 virus.

Nuvaxovid JN.1 is given to individuals 12 years of age and older.

The vaccine causes the immune system (the body's natural defences) to produce antibodies and specialised white blood cells that work against the virus, to give protection against COVID-19. None of the ingredients in this vaccine can cause COVID-19.

2. What you need to know before you receive Nuvaxovid JN.1

Nuvaxovid JN.1 should not be given
- if you are allergic to the active substance or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor, pharmacist, or nurse before you are given Nuvaxovid JN.1 if:
- you have ever had a severe or life-threatening allergic reaction after receiving any other vaccine injection or after you were given Nuvaxovid or Nuvaxovid JN.1 in the past,
- you have ever fainted following any needle injection,
- you have a high fever (over 38°C) or severe infection. However, you can have your vaccination if you have a mild fever or upper airway infection like a cold,
- you have bleeding problems, you bruise easily or you use a medicine to prevent blood clots,
- your immune system does not work properly (immunodeficiency) or you are taking medicines that weaken the immune system (such as high-dose corticosteroids, immunosuppressants, or cancer medicines).

There is an increased risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) after vaccination with Nuvaxovid, see section 4. These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days.
Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist, or nurse before you are given Nuvaxovid JN.1.

As with any vaccine, a single dose of Nuvaxovid JN.1 may not fully protect all those who receive it and it is not known how long you will be protected.

Children

Nuvaxovid JN.1 is not recommended for children aged below 12 years. Currently, there is no information available on the use of Nuvaxovid JN.1 in children younger than 12 years of age.

Other medicines and Nuvaxovid JN.1

Tell your doctor, pharmacist, or nurse if you are taking, have recently taken, or might take any other medicines or vaccines.

Pregnancy and breastfeeding

If you are pregnant or breastfeeding, think you may be pregnant, or are planning to have a baby, ask your doctor, pharmacist, or nurse for advice before you receive this vaccine.

Driving and using machines

Some of the side effects of Nuvaxovid JN.1 listed in section 4 (Possible side effects) may temporarily reduce your ability to drive and use machines (for example, feeling faint or lightheaded or feeling very tired).

Do not drive or use machines if you are feeling unwell after vaccination. Wait until any effects of the vaccine have worn off before you drive or use machines.

Nuvaxovid JN.1 contains sodium and potassium

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

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

3. How Nuvaxovid JN.1 is given

Individuals 12 years of age and older
Nuvaxovid JN.1 will be given to you as a single dose 0.5 mL injection.

If you were previously vaccinated with a COVID-19 vaccine, Nuvaxovid JN.1 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

Your doctor, pharmacist, or nurse will inject the vaccine into a muscle, usually in your upper arm.

During and after each injection of the vaccine, your doctor, pharmacist, or nurse will watch over you for around 15 minutes to monitor for signs of an allergic reaction.

Additional doses (0.5 mL) of Nuvaxovid JN.1 may be administered at the discretion of your physician, taking into consideration your clinical conditions in line with national recommendations.

Immunocompromised individuals
If your immune system does not work properly additional doses may be administered in line with national recommendations.

4. Possible side effects

Like all medicines, this vaccine can cause side effects, although not everybody gets them. Most side effects go away within a few days of appearing. If symptoms persist, contact your doctor, pharmacist or nurse.

As with other vaccines, you may feel pain or discomfort at the injection site, or you may see some redness and swelling at this site. However, these reactions usually clear up within a few days.

Get **urgent** medical attention if you get any of the following signs and symptoms of an allergic reaction:
- feeling faint or light-headed
- changes in your heartbeat
- shortness of breath
- wheezing
- swelling of your lips, face, or throat
- hives or rash
- nausea or vomiting
- stomach pain

Talk to your doctor or nurse if you develop any other side effects. These can include:

Very common (may affect more than 1 in 10 people):
- headache
- feeling sick (nausea) or getting sick (vomiting)
- muscle ache
- joint pain
- tenderness or pain where the injection is given
- feeling very tired (fatigue)
- generally feeling unwell

Common (may affect up to 1 in 10 people):
- redness where the injection is given
- swelling where the injection is given
- fever (>38°C)
- pain or discomfort in the arm, hand, leg and/or foot (pain in the extremity)

Uncommon (may affect up to 1 in 100 people):
- enlarged lymph nodes
- high blood pressure
- itchy skin, rash or hives
- redness of the skin
- itchy skin where the injection is given
- chills

Rare (may affect up to 1 in 1000 people):
- warmth where the injection is given

Not known (cannot be estimated from available data):
- severe allergic reaction
- unusual feeling in the skin, such as tingling or a crawling feeling (paraesthesia)
- decreased feeling or sensitivity, especially in the skin (hypoaesthesia)
- inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis), which can result in breathlessness, palpitations or chest pain

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V and include batch/Lot number if available. By reporting side effects, you can help provide more information on the safety of this vaccine.

5. How to store Nuvaxovid JN.1

Keep this medicine out of the sight and reach of children.

Your doctor, pharmacist, or nurse is responsible for storing this vaccine and disposing of any unused product correctly.

Information about storage, expiry, use and handling are described in the section intended for healthcare professionals at the end of the package leaflet.

6. Contents of the pack and other information

What Nuvaxovid JN.1 contains

- One dose (0.5 mL) Nuvaxovid JN.1 contains 5 micrograms of SARS-CoV-2 (Omicron JN.1) spike protein* and is adjuvanted with Matrix-M.

  *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.

- Matrix-M is included in this vaccine as an adjuvant. Adjuvants are substances included in certain vaccines to accelerate, improve, and/or prolong the protective effects of the vaccine. Matrix-M adjuvant contains Fraction-A (42.5 micrograms) and Fraction-C (7.5 micrograms) of *Quillaja saponaria* Molina extract per 0.5 mL dose.

- The other ingredients (excipients) included in Nuvaxovid JN.1 are:
  - Disodium hydrogen phosphate heptahydrate
  - Sodium dihydrogen phosphate monohydrate
  - Disodium hydrogen phosphate dihydrate
  - Sodium chloride
  - Polysorbate 80
  - Cholesterol
  - Phosphatidylcholine (including all-rac-α-Tocopherol)
  - Potassium dihydrogen phosphate
  - Potassium chloride
  - Sodium hydroxide (for the adjustment of pH)

- Hydrochloric acid (for the adjustment of pH)
- Water for injections

What Nuvaxovid JN.1 looks like and contents of the pack

- The dispersion is colourless to slightly yellow, clear to mildly opalescent (pH 7.2).
- 0.5 mL of dispersion for injection in a pre-filled syringe with a plunger stopper and a tip cap, without a needle or co-packed with a separate needle.
- Pack size:
    - 10 pre-filled syringes.
    - 1 pre-filled syringe
    - 1 pre-filled syringe with a separate needle
- Each syringe contains 1 dose of 0.5 mL.

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This leaflet was last revised in.

Scan the code with a mobile device to get the package leaflet in different languages.

Or visit the URL: https://www.NovavaxCovidVaccine.com

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

The following information is intended for healthcare professionals only:

Administer Nuvaxovid JN.1 intramuscularly, preferably into the deltoid muscle of the upper arm, as a single dose.

For individuals who have previously been vaccinated with a COVID-19 vaccine, Nuvaxovid JN.1 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

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

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.

Handling instructions and administration

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

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.
- The pre-filled syringe should be stored in a refrigerator (2°C – 8°C) and kept within the outer carton to protect from light.
- Immediately prior to use, remove the pre-filled syringe from the carton in the refrigerator.
- Each pre-filled syringe is for single use only.

Inspect the pre-filled syringe

- Do not shake the pre-filled syringe.
- Each pre-filled syringe contains a colourless to slightly yellow, clear to mildly opalescent dispersion.
- Visually inspect the contents of the pre-filled syringe for visible particulate matter and/or discolouration prior to administration. Do not administer the vaccine if either are present.
- Do not use the pre-filled syringe if the tip cap has been removed or is missing.
- Do not use the pre-filled syringe if it leaks or there are some visible cracks on it.

Administer the pre-filled syringe

- Pre-filled syringe without a needle
    - Needles are not included in the pre-filled syringe cartons.
    - Use a sterile needle of the appropriate size for intramuscular injection (21-gauge or thinner needles)
- Pre-filled syringe with a separate needle
    - Use a needle included in the pack.
- With tip cap of the pre-filled syringe upright, remove tip cap twisting counter-clockwise until tip cap releases. Remove tip cap in a slow, steady motion. Avoid pulling tip cap while twisting.

- Attach the needle by twisting in a clockwise direction until the needle fits securely on the syringe.
- Uncap the needle when ready for administration.
- Administer the entire dose intramuscularly, preferably in the deltoid muscle of the upper arm.

Discard

- Discard the pre-filled syringe after administration.
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Disposal

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