Date: 5 January 2023
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report
Extension of therapeutic indication

Nuvaxovid

International non-proprietary name: SARS CoV-2 recombinant spike protein (rS NVX-CoV2373)

Pharmaceutical form: dispersion for injection

Dosage strength(s): 10 doses of 0.5 mL each, with 5 µg per 0.5 mL

Route(s) of administration: intramuscular injection

Marketing Authorisation Holder: Future Health Pharma GmbH

Marketing Authorisation No.: 68473

Decision and Decision date: extension of therapeutic indication temporarily approved in accordance with Art. 9a TPA on 02.09.2022

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GLP	Good laboratory practice
HPLC	High performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International nonproprietary name
ITT	Intention-to-treat
LoQ	List of questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetic
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetic
PSP	Pediatric study plan (US-FDA)
RMP	Risk Management Plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

OPEN project EMA
Swissmedic has been participating in the EMA's OPEN project. Further information at: *EMA COVID-19 assessments 'OPEN' to non-EU regulators | European Medicines Agency (europa.eu).*

Extension(s) of the therapeutic indication(s)
The applicant requested to add or change the indication in accordance with Article 23 TPO.

2.2 Indication and Dosage

2.2.1 Requested Indication

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.

2.2.2 Approved Indication

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.

2.2.3 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	1 July 2022
Formal control completed	6 July 2022
Predecision	19 August 2022
Answers to Predecision	28 August 2022
Final Decision	2 September 2022
Decision	approval (temporary authorisation in accordance with Art. 9a TPA)

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3 Medical Context

Several vaccines have been developed and approved using various technologies to confer immunity against COVID-19 based on the ancestral SARS-CoV-2 strain. Although clinical studies and real-world evidence have shown that these vaccines are highly effective in reducing severe disease and death due to COVID-19, there are also signs that their protection may be waning after primary vaccination since vaccination campaigns began in late 2020. In addition, several SARS-CoV-2 variants have emerged with changes in the S protein and other regions, enabling them to partially avoid antibody neutralisation in vaccinated persons.
At the time of the review the Federal Office of Public Health and the Federal Vaccination Commission recommended vaccination for all young people aged 12 and above. Two mRNA vaccines currently have temporary authorisation for adolescents in Switzerland.

4 Nonclinical Aspects

The applicant did not submit new nonclinical studies to support the requested extension of the indication to adolescents 12 years of age and older. This is considered acceptable since immune responses and safety are expected to be similar in adolescents and adults for the same dosing scheme.
No nonclinical studies were conducted to assess the requested booster dose in adults following a primary immunisation with either Nuvaxovid or other COVID vaccines, such as mRNA or adenoviral vector vaccines. This is considered acceptable since immune responses and safety are expected to be similar after a primary immunisation with two doses and a subsequent booster.
An environmental risk is not expected from a protein-based vaccine such as Nuvaxovid.
From the nonclinical point of view, there are no objections to approval of the proposed extension to adolescents and the booster.

5 Clinical and Clinical Pharmacology Aspects

The evaluation of the clinical data of this application for indication extension to adolescents 12 to <18 years of age has been carried out in reliance on previous regulatory decisions by the EMA. The available EMA assessment reports and the respective product information for Nuvaxovid (Assessment Report EMA/637822/2022, dated 23 June 2022) were used as a basis for the clinical evaluation.

As requested by Swissmedic, the applicant additionally submitted immunogenicity data from the pivotal Study 2019nCoV-301 for the currently circulating Omicron variants (including BA.5).
Although the provided graphical presentation of the immunogenicity data referred to adults, a similar (or even higher) immune response can be expected in adolescents. Based on the anti-spike IgG and ACE-2 (angiotensin-converting enzyme 2) receptor binding inhibition, an activity against the BA.5 lineage can be expected. Data on in vitro neutralisation, however, were not provided. The study report describing the above data will be submitted (clinical post-marketing requirement). Efficacy data were not available for the circulating Omicron variants.

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6 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Nuvaxovid was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ 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 new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.
Nuvaxovid is temporarily authorised – see section Pharmacological Properties.

Nuvaxovid, dispersion for injection

Composition

Active substances

One dose (0.5 mL) contains 5 micrograms of the 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.

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) and water for injections
Adjuvant (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.
Cholesterol, phosphatidylcholine (including all-rac-α-Tocopherol), potassium dihydrogen phosphate, potassium chloride, disodium hydrogen phosphate dihydrate, sodium chloride and water for injections

0.5 mL dispersion contains 4 mg sodium and 0.003 mg potassium.

Pharmaceutical form and active substance quantity per unit

Dispersion for injection (injection).
The dispersion is colourless to slightly yellow, clear to mildly opalescent (pH 7.2)
This is a multidose vial which contains 10 doses of 0.5 mL

Indications/Uses

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.

Dosage/Administration

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 “Properties/Effects”.
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 18 years of age and older

Nuvaxovid (0.5 mL) may be administered intramuscularly as a homologous booster dose approximately 6 months after the second dose of the primary series of Nuvaxovid in individuals 18 years of age and older.
In addition, there are data that Nuvaxovid may be administered intramuscularly as a heterologous booster dose following a primary series of various COVID-19 vaccines (see “Properties/Effects”).

Elderly patients

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

Children and adolescents

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

Mode 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 ”Warnings and precautions”.
For instructions on handling and disposal of the vaccine, see section “Other information”.

Contraindications

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

Warnings and precautions

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.

Hypersensitivity and anaphylaxis

Events of anaphylaxis have been reported with COVID-19 vaccines including Nuvaxovid Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine.

Close observation for at least 15 minutes is recommended following vaccination. A second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose of Nuvaxovid.

Myocarditis and pericarditis

Very rare cases of myocarditis and pericarditis have been reported following the use of Nuvaxovid. 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.

Other precautions

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 mg) per dose, that is to say, essentially 'potassium-free'.

Interactions

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 "Undesirable effects" and section "Properties/Effects".

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.

Pregnancy, 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 "Preclinical data".

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

Lactation

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 "Preclinical data".

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 "Undesirable effects" may temporarily affect the ability to drive or use machines.

Undesirable effects

Summary of the safety profile

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

The safety of Nuvaxovid was evaluated from an interim analysis of pooled data from 5 ongoing clinical trials conducted in Australia, South Africa, the United Kingdom, the United States and Mexico. At the time of the analysis, a total of 49,950 participants aged 18 years and older received at least one dose for the two-dose primary series of Nuvaxovid (n=30,058) or placebo (n=19,892). At the time of vaccination, the median age was 48 years (range 18 to 95 years). The median duration of follow-up was 70 days post-Dose 2, with 32,993 (66%) participants completing more than 2 months follow-up post-Dose 2.

Of the pooled reactogenicity data, which includes participants aged 18 years and older enrolled in the two phase 3 studies who received any dose of Nuvaxovid (n=20,055) or placebo (n=10,561), the most frequent adverse reactions were injection site tenderness (75%), injection site pain (62%), fatigue (53%), myalgia (51%), headache (50%), malaise (41%), arthralgia (24%), and nausea or vomiting (15%). Adverse reactions were usually mild to moderate in severity with a median duration of less than or equal to 2 days for local events and less than or equal to 1 day for systemic events following vaccination.

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

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

Licensed inactivated seasonal influenza vaccines were co-administered to participants on the same day as Dose 1 of Nuvaxovid (n=217) or placebo (n=214) in the opposite deltoid muscle of the arm in 431 participants enrolled in an exploratory Phase 3 (2019nCoV-302) sub-study. The frequency of local and systemic adverse reactions in the influenza sub-study population was higher than in the main study population following Dose 1 in both Nuvaxovid and placebo recipients.

Adolescents 12 through 17 years of age

The safety of Nuvaxovid in adolescents was evaluated in an interim analysis of the paediatric expansion portion of an ongoing Phase 3 multicentre, randomised, observer-blinded, placebo-controlled study (Study 2019nCoV-301). Safety data were collected in 2,232 participants 12 through 17 years of age, with and without evidence of prior SARS CoV-2 infection, in the United States who received at least one dose of Nuvaxovid (n=1,487) and placebo (n=745). Demographic characteristics were similar between the two groups.

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 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.

List of adverse reactions

The adverse reactions should be arranged according to MedDRA system organ classes and the conventional frequencies as follows:
"very common" (≥1/10), "common" (≥1/100, <1/10), "uncommon" (≥1/1,000, <1/100), "rare" (≥1/10,000, <1/ 1,000), "very rare" (<1/10,000), "not known" (frequency cannot be estimated from the available data)

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

System Organ Class	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Not known (frequency cannot be estimated from the available data)
Blood and lymphatic system disorders			Lymphadenopathy	
Immune system disorders				Anaphylaxis[f]
Nervous system disorders	Headache			Paraesthesia[f] Hypoaesthesia[f]
Cardiac disorders				Myocarditis[f] Pericarditis[f]
Vascular disorders			Hypertension[d]	
Gastrointestinal disorders	Nausea or vomiting[a]			
Skin and subcutaneous tissue disorders			Rash Erythema Pruritus Urticaria	
Musculoskeletal and connective tissue disorders	Myalgia[a] Arthralgia[a]			

General disorders and administration site conditions	Injection site tenderness[a] Injection site pain[a] Fatigue[a] Malaise[a,b]	Injection site redness[a,c] Injection site swelling[a] Pyrexia[e] Chills Pain in extremity	Injection site pruritus	

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 adolescent aged 12 through to 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

f Adverse reaction determined post-authorisation

Description of specific adverse reactions and additional information

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.

Participants 18 years of age and older – after homologous booster dose

The safety and immunogenicity of a booster dose of Nuvaxovid was evaluated in an ongoing Phase 2 randomised, placebo-controlled, observer-blinded clinical study (Study 2019nCoV-101, Part 2) conducted in participants 18 to 84 years of age. A total of 254 participants received two doses of Nuvaxovid (0.5 mL 3 weeks apart) as the primary vaccination series. A subset of 105 participants (Safety Analysis Set) were randomised to receive a booster dose of Nuvaxovid approximately 6 months after receiving Dose 2 of the primary series and received at least 1 dose of study vaccine; 104 of the 105 participants received Nuvaxovid (Full Analysis Set).

Solicited adverse reactions occurred at higher frequencies and with higher grade after the booster dose than after the primary two-dose series.

The most frequent solicited adverse reactions were injection site tenderness (81%), fatigue (63%), injection site pain (55%), muscle pain (51%), malaise (47%) and headache (46%), joint pain (29%), and fever (17%) with a median duration of 1 to 3 days following vaccination.

In a second ongoing Phase 2a/b randomised, placebo-controlled, observer-blinded clinical study conducted in South Africa (Study 2019nCoV-501), the immunogenicity and safety of a booster dose of Nuvaxovid was evaluated in healthy HIV-negative participants 18 to 84 years of age (Cohort 1) and

medically stable people living with HIV (PLWH) 18 to 64 years of age (Cohort 2). Overall, 1,898 participants (Safety Analysis Set) received a booster dose of Nuvaxovid approximately 6 months after receiving the second dose of the two-dose primary series. Solicited adverse reactions were not collected following the booster dose.

Participant 18 years of age and older – after heterologous booster dose
The safety of a Nuvaxovid third dose in individuals who completed a primary vaccination with another authorized or approved COVID-19 vaccine (heterologous booster dose) has been evaluated in an independent, multicentric randomized, controlled, Phase 2, investigator-initiated trial conducted in the United Kingdom (ISRCTN 73765130). Review of the adverse reactions over the 28 days following a Nuvaxovid booster dose in 229 participants did not identify any new safety concerns, as compared with adverse reactions reported following two doses of Nuvaxovid given as a primary series.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

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

Properties/Effects

ATC code

J07BX03

Mechanism of action

Nuvaxovid is composed of purified full-length SARS-CoV-2 recombinant spike (S) protein that is stabilised in its prefusion conformation. The addition of the saponin-based Matrix-M adjuvant facilitates activation of the cells of the innate immune system, which enhances the magnitude of the S protein-specific immune response. The 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.

Pharmacodynamics

Not applicable.

Clinical efficacy

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) – Two-Dose Primary Series

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

Participants 18 years of age and older

Upon enrolment, in the adult main study, participants were stratified by age (18 to 64 years and ≥ 65 years) and assigned in a 2:1 ratio to receive Nuvaxovid or placebo. The study excluded participants who were significantly immunocompromised due to immunodeficiency disease; active cancer on chemotherapy; received chronic immunosuppressive therapy or received immunoglobulin or blood-derived products within 90 days; were pregnant or breastfeeding; or had a history of laboratory-confirmed diagnosed COVID-19. Participants with clinically stable underlying comorbidity were included as were participants with well-controlled HIV infection.

Enrolment of adults completed in February 2021. Participants will be followed for up to 24 months after the second dose for assessments of safety, and efficacy against COVID-19. Following collection of sufficient safety data to support application for emergency use authorisation, initial recipients of placebo were invited to receive two injections of Nuvaxovid 21 days apart and initial recipients of Nuvaxovid to receive two injections of placebo 21 days apart (“blinded crossover”). All participants were offered the opportunity to continue to be followed in the study.

The primary efficacy analysis population (referred to as the Per-Protocol Efficacy [PP-EFF] analysis set) included 25,452 participants who received either Nuvaxovid (n=17,312) or placebo (n=8,140), received two doses (Dose 1 on day 0; Dose 2 at day 21, median 21 days [IQR 21-23], range 14-60), did not experience an exclusionary protocol deviation, and did not have evidence of SARS-CoV-2 infection through 7 days after the second dose.

Demographic and baseline characteristics were balanced amongst participants who received Nuvaxovid and those who received placebo. In the PP-EFF analysis set for participants who received Nuvaxovid, the median age was 47 years (range: 18 to 95 years); 88% (n=15,264) were 18 to 64 years old and 12% (n=2,048) were aged 65 and older; 48% were female; 94% were from the United States and 6% were from Mexico; 76% were White, 11% were Black or African American, 6% were American Indian (including Native Americans) or Alaskan Native, and 4% were Asian; 22% were Hispanic or Latino. At least one pre-existing comorbidity or lifestyle characteristic associated with an increased risk of severe COVID-19 was present in 16,493 (95%) participants. Comorbidities included:

obesity (body mass index (BMI) ≥ 30 kg/m2); chronic lung disease; diabetes mellitus type 2, cardiovascular disease; chronic kidney disease; or human immunodeficiency virus (HIV). Other high-risk characteristics included age ≥65 years (with or without comorbidities) or age <65 years with comorbidities and/or living or working conditions involving known frequent exposure to SARS-CoV-2 or to densely populated circumstances.

COVID-19 cases were confirmed by polymerase chain reaction (PCR) through a central laboratory.

Vaccine efficacy is presented in Table 2.

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

Subgroup	Nuvaxovid			Placebo			% Vaccine Efficacy (95% CI)
	Partici-pants N	COVID-19 cases n (%)[2]	Incidence Rate Per Year Per 1,000 People[2]	Partici-pants N	COVID-19 cases n (%)[3]	Incidence Rate Per Year Per 1,000 People[2]	
Primary efficacy endpoint							
All participants	17,312	14 (0.1)	3.26	8,140	63 (0.8)	34.01	90.4% (82.9, 94.6)[3,4]

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

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

[3] Based on log-linear model of PCR-confirmed COVID-19 infection incidence rate using Poisson regression with treatment group and age strata as fixed effects and robust error variance, where VE = 100 × (1 – relative risk) (Zou 2004).

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

Vaccine efficacy of Nuvaxovid to prevent the onset of COVID-19 from seven days after Dose 2 was 90.4% (95% CI 82.9, 94.6). No cases of severe COVID-19 were reported in the 17,312 Nuvaxovid participants compared with 4 cases of severe COVID-19 reported in the 8,140 placebo recipients in the PP-EFF analysis set.

Subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates for male and female participants and racial groups, and across participants with medical comorbidities associated with high risk of severe COVID-19. There were no meaningful differences in overall vaccine efficacy in participants who were at increased risk of severe COVID-19 including those with 1 or more comorbidities that increase the risk of severe COVID-19 (e.g., BMI ≥ 30 kg/m2, chronic lung disease, diabetes mellitus type 2, cardiovascular disease, and chronic kidney disease).

Efficacy results reflect enrolment that occurred during the time period when strains classified as Variants of Concern or Variants of Interest were predominantly circulating in the two countries (US and Mexico) where the study was conducted. Sequencing data were available for 61 of the 77 endpoint cases (79%). Of these, 48 out of 61 (79%) were identified as Variants of Concern or Variants of Interest. The most common Variants of Concern identified were: Alpha with 31/61 cases (51%),

Beta (2/61, 4%) and Gamma (2/61, 4%), while the most common Variants of Interest were Iota with 8/61 cases (13%), and Epsilon (3/61, 5%).

Efficacy in Adolescents 12 through 17 years of age

The assessment of efficacy and immunogenicity of Nuvaxovid in adolescent participants 12 through 17 years of age occurred in the United States in the ongoing descriptive, paediatric expansion portion of the Phase 3 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. Demographic characteristics were similar among participants who received NUVAXOVID and those who received placebo.

COVID-19 was defined as first episode of PCR-confirmed mild, moderate, or severe COVID-19 with at least one or more of the predefined symptoms within each severity category. Mild COVID-19 was defined as fever, new onset cough or at least 2 or more additional COVD-19 symptoms.
There were 20 cases of PCR-confirmed symptomatic mild COVID-19 (Nuvaxovid, n=6 [0.5%]; placebo, n=14 [2.4%]) resulting in a point estimate of efficacy of 79.5% (95% CI: 46.8%, 92.1%).
At the time of this analysis, the Delta (B.1.617.2 and AY lineages) variant of concern (VOC) was the predominant variant circulating in the US and accounted for all cases from which sequence data are available (11/20, 55%).

Immunogenicity in Adolescents 12 through 17 years of age

An analysis of the SARS-CoV-2 neutralising antibody response 14 days after Dose 2 (Day 35) was conducted in adolescent participants seronegative to anti-SARS-CoV-2 nucleoprotein (NP) or PCR-negative at baseline. Neutralising antibody responses were compared with those observed in seronegative/PCR-negative adult participants aged 18 through 25 years from the adult main study (Per Protocol Immunogenicity (PP-IMM) Analysis Set) as shown in Table 3. Noninferiority required that the following three criteria be 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%.

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	Pediatric 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 coronavirus2.

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

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

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

n1 = number of participants in adult main study (18 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) - Two-Dose Primary Series

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

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

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

Demographic and baseline characteristics were balanced amongst participants who received Nuvaxovid and participants who received placebo. In the PP-EFF analysis set for participants who received Nuvaxovid, median age was 56.0 years (range: 18 to 84 years); 72% (n=5,067) were 18 to 64 years old and 28% (n=1,953) were aged 65 to 84; 49% were female; 94% were White; 3% were Asian; 1% were multiple races, <1% were Black or African American; and <1% were Hispanic or Latino; and 45% had at least one comorbid condition.

Table 4: Vaccine efficacy analysis of PCR-confirmed COVID-19 with onset at least 7 days after the second vaccination - (PP-EFF population): Study 2 (2019nCoV-302)

	Nuvaxovid			Placebo			
Subgroup	Participants N	COVID-19 cases n (%)	Incidence Rate Per Year Per 1,000 People[1]	Participants N	COVID-19 cases n (%)	Incidence Rate Per Year Per 1,000 People[1]	% Vaccine Efficacy (95% CI)
Primary efficacy endpoint							
All participants	7,020	10 (0.1)	6.53	7,019	96 (1.4)	63.43	89.7% (80.2, 94.6)[2,3]
Subgroup analyses of the primary efficacy endpoint							
18 to 64 years of age	5,067	9 (0.2)	12.30	5,062	87 (1.7)	120.22	89.8% (79.7, 94.9)[2]
65 to 84 years of age	1,953	1 (0.10)[2]	---	1,957	9 (0.9)[2]	---	88.9% (20.2, 99.7)[4]

1 Mean disease incidence rate per year in 1000 people.

2 Based on Log-linear model of occurrence using modified Poisson regression with logarithmic link function, treatment group and strata (age-group and pooled region) as fixed effects and robust error variance [Zou 2004].

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

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

These results reflect enrolment that occurred during the time period when the B.1.1.7 (Alpha) variant was circulating in the UK. Identification of the Alpha variant was based on S gene target failure by PCR. Data were available for 95 of the 106 endpoint cases (90%). Of these, 66 out of 95 (69%) were identified as the Alpha variant with the other cases classified as non-Alpha.
No cases of severe COVID-19 were reported in the 7,020 Nuvaxovid participants compared with 4 cases of severe COVID-19 reported in the 7,019 placebo recipients in the PP-EFF analysis set.

Licensed seasonal influenza vaccine co-administration sub-study

Overall, 431 participants were co-vaccinated with inactivated seasonal influenza vaccines; 217 sub-study participants received Nuvaxovid and 214 received placebo. Demographic and baseline

characteristics were balanced amongst participants who received Nuvaxovid and participants who received placebo. In the per-protocol immunogenicity (PP-IMM) analysis set for participants who received Nuvaxovid (n=191), median age was 40 years (range: 22 to 70 years); 93% (n=178) were 18 to 64 years old and 7% (n=13) were aged 65 to 84; 43% were female; 75% were White; 23% were multiracial or from ethnic minorities; and 27% had at least one comorbid condition. Co-administration resulted in no change to influenza vaccine immune responses as measured by hemagglutination inhibition (HAI) assay. A 30% reduction in antibody responses to Nuvaxovid was noted as assessed by an anti-spike IgG assay with seroconversion rates similar to participants who did not receive concomitant influenza vaccine (see section ”Interactions” and section ”Undesirable effects”).

Study 3 (2019nCoV-501) – Two-Dose Primary Series

Study 3 is an ongoing Phase 2a/b, multicentre, randomised, observer-blinded, placebo-controlled study in HIV-negative participants 18 to 84 years of age and people living with HIV (PLWH) 18 to 64 years of age in South Africa. PLWH were medically stable (free of opportunistic infections), receiving highly active and stable antiretroviral therapy, and having an HIV-1 viral load of < 1000 copies/mL.
Enrolment was completed in November 2020.
The primary efficacy analysis set (PP-EFF) included 2,770 participants who received either Nuvaxovid (n=1,408) or placebo (n=1,362), received two doses (Dose 1 on day 0; Dose 2 on day 21), did not experience an exclusionary protocol deviation, and did not have evidence of SARS-CoV-2 infection through 7 days after the second dose.
Demographic and baseline characteristics were balanced amongst participants who received Nuvaxovid and participants who received placebo. In the PP-EFF analysis set for participants who received Nuvaxovid, median age was 28 years (range: 18 to 84 years); 40% were female; 91% were Black/African American; 2% were White; 3% were multiple races, 1% were Asian; and 2% were Hispanic or Latino; and 5.5% were HIV-positive.
A total of 147 symptomatic mild, moderate, or severe COVID-19 cases among all adult participants, seronegative (to SARS-CoV-2) at baseline, were accrued for the complete analysis (PP-EFF Analysis Set) of the primary efficacy endpoint, with 51 (3.62%) cases for Nuvaxovid versus 96 (7.05%) cases for placebo. The resultant vaccine efficacy of Nuvaxovid was 48.6% (95% CI: 28.4, 63.1).
These results reflect enrolment that occurred during the time period when the B.1.351 (Beta) variant was circulating in South Africa.

Immunogenicity after booster dose in participants 18 years of age and older
The safety and immunogenicity of a homologous booster dose of Nuvaxovid was evaluated in an ongoing Phase 2 randomised, observer-blinded, placebo-controlled clinical study administered as a single booster dose (Study 2019nCoV-101, Part 2) in healthy adult participants aged 18 to 84 years of age who were seronegative to SARS-CoV-2 at baseline.

A total of 254 participants (Full Analysis Set) received two doses of Nuvaxovid (0.5 mL, 5 micrograms 3 weeks apart) as the primary vaccination series. A subset of 104 participants received a booster dose of Nuvaxovid approximately 6 months after receiving Dose 2 of the primary series.
A single booster dose of Nuvaxovid induced an approximate 34-fold increase in the immune response against the Wuhan (ancestral) strain 28 days after receipt of the dose (Day 217) with serum anti-spike IgG geometric mean level (GMEU) of 204,367 EU compared to a GMEU of 6,064 EU pre-booster (Day 189) and an approximate 4.7-fold increase from peak GMEU (43,905 EU), 14 days following Dose 2 of the primary series. An approximate 96-fold increase in neutralising antibodies was shown from a geometric mean titer (GMT) of 63 pre-booster (Day 189) to a GMT of 6,023 post-booster (Day 217) and an approximate 4.1-fold increase from a peak GMT (14 days post-Dose 2) of 1,470.
A fit-for-purpose, but un-validated assay comparing wild –type microneutralisation (MN99) GMTs (n = 32) two weeks after the primary to four weeks after booster vaccination demonstrated a 15.4-fold, 14.0-fold and 3.5-fold increase for the Ancestral, Delta and Omicron (B.1.1.529) variants, respectively.

In Study 3, an ongoing Phase 2a/b randomised, observer-blinded, placebo-controlled study, the safety and immunogenicity of booster dose was evaluated in healthy HIV-negative adult participants 18 to 84 years of age and medically stable PLWH 18 to 64 years of age who were seronegative to SARS-CoV-2 at baseline. A total of 1,173 participants (PP-IMM Analysis Set) received a booster dose of Nuvaxovid approximately 6 months after completion of the primary series of Nuvaxovid (Day 201). An approximate 31-fold increase was shown in serum IgG GMT assessed at Day 236 (111,066 EU) from the pre-boost GMT at Day 201 (3,632 EU). An approximate 3.6-fold increase was demonstrated from peak GMT (30,756 EU) at Day 35 following completion of the primary series.
An approximate 52-fold increase in neutralising antibodies was shown from a GMT of 69 pre-booster (Day 201) to a GMT of 3,600 post-booster (Day 236) and an approximate 5.2-fold increase from a peak GMT (14 days post-Dose 2) of 694.

Published data from an independent, multicentre, randomised, controlled, Phase 2 investigator-initiated trial (COV-BOOST, ISRCTN 73765130) assessed the safety and immunogenicity of seven COVID-19 vaccines given as a third dose (heterologous booster) following completion of a primary vaccination series with another authorised COVID-19 vaccine in the UK. In adults aged 30 years and older in good physical health 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 against the wild-type virus and IgG antibodies against wild-type Spike protein were assessed prior to the booster dose and 28 days post-booster dose. Within the group assigned to receive Nuvaxovid, 115 participants had received a two-dose primary series of ChAdOx1 nCov-19 and 114 participants had 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. It is noted that the incremental increase in antibody concentrations was lower following a third (booster) dose with NUVAXOVID than following mRNA vaccines.

Elderly patients

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).

Paediatrics

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 “Dosage/Administration” for information on paediatric use.

Temporary authorisation

The medicinal product Nuvaxovid has been granted temporary authorisation as the data was incomplete at the time the authorisation application was assessed (Art. 9a TPA). The temporary authorisation is contingent on the timely fulfilment of conditions. After they have been met, the temporary authorisation can be transformed into an ordinary authorisation.

Pharmacokinetics

Absorption

Not applicable.

Distribution

Not applicable.

Metabolism

Not applicable.

Elimination

Not applicable.

Preclinical 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

In vitro genotoxicity studies were conducted with the Matrix-M adjuvant. The adjuvant was shown to be non-genotoxic.

Carcinogenicity

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.

Other information

Incompatibilities

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

Shelf life

Unopened vial
2°C to 8°C, protected from light.
Do not use this medicine after the expiry date marked as "EXP" on the pack.
Punctured vial
Chemical and physical in-use stability has been demonstrated for 6 hours at 2°C to 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.

Special precautions for storage

Store in a refrigerator (2°C to 8°C) and do not freeze.
Keep the vials in the outer carton in order to protect the contents from light.
Keep out of the reach of children.

Instructions for handling

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 6 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 ten (10) doses 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:

- Nuvaxovid does not contain a preservative. Store the opened vial between 2°C to 25°C for up to 6 hours after first puncture, see section “Shelf life”.

Discard:

- Discard this vaccine if not used within 6 hours after first puncture of the vial, see section “Shelf life”.

Disposal:

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

Authorisation number

68473 (Swissmedic)

Packs

Each vial contains 10 doses of 0.5 mL.
Pack size: 10 multidose vials [B].

Marketing authorisation holder

Future Health Pharma GmbH, 8620 Wetzikon ZH

Manufacturer

Novavax CZ a.s., Bohumil 138, Jevany, 28163, Czechia

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