EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 June 2022
EMA/637822/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: Nuvaxovid

Common name: COVID-19 vaccine (recombinant, adjuvanted)

Procedure No. EMEA/H/C/005808/II/0009

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted and personal data anonymised.

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List of abbreviations

+ssRNA	Positive-sense single-stranded RNA
Ab	Antibody
AE	Adverse event
AESI	Adverse event of special interest
AMI	Acute myocardial infarction
ANCOVA	Analysis of covariance
ARDS	Acute respiratory distress syndrome
BiPAP	Bi-level positive airway pressure
CDC	US Centers for Disease Control and Prevention
CHMP	Committee for Medicinal Products for Human use
CI	Confidence interval
CMA	Conditional Marketing Authorisation
COVID-19	Coronavirus disease 2019
CPAP	Continuous positive airway pressure
CRO	Contract research organisation
CRP	C-reactive protein
CT	Computed tomography
DVT	Deep vein thrombosis
E	Envelope
EC	European Commission
ECDC	European Centre for Disease Prevention and Control
ECMO	Extracorporeal membrane oxygenation
eCRF	Electronic Case Report Forms
eDiary	Electronic diary
ELISA	Enzyme-linked immunosorbent assay
EPAR	European Public Assessment Report
EoS	End of study
ER	Emergency room
ETF	COVID-19 EMA pandemic Task Force
EU	European Union
EUA	US FDA Emergency Use Authorisation
EURD	European reference date
FAS	Full Analysis Set
GCP	Good Clinical Practice
GMEU	Geometric mean ELISA unit(s)
GMFR	Geometric mean fold-rise
GMT	Geometric mean titer(s)
hACE2	Human angiotensin converting enzyme 2
ICU	Intensive care unit
IgG	Immunoglobulin G
IL-6	Interleukin 6
ITT	Intent-to-treat
IU	International Units
IWRS	interactive web response system
LDH	Lactate dehydrogenase
LLoQ	Lower limit of quantification
LRTI	Lower respiratory tract infection
M	Membrane

MAAE	Medically attended adverse event
MAH	Marketing authorisation holder
MERS-CoV	Middle East respiratory syndrome coronavirus
MIS-C	Multisystem inflammatory syndrome in children
MLE	Maximum likelihood estimator
mmHg	Millimetres of mercury
MN	Microneutralisation
MN50	50% microneutralisation
MSSR	Monthly summary safety report
N	Nucleocapsid
NAAT	Nucleic Acid Amplification Test
nAb	Neutralising antibody(ies)
NI	Non-inferiority
NIPPV	Non-invasive positive pressure ventilation
NIV	Non-invasive ventilation
NP	Nucleoprotein
PaO2/FiO2	arterial oxygen partial pressure to fractional inspired oxygen
PCR	Polymerase chain reaction
PE	Pulmonary embolism
PI	Product information
PIMMCs	Potential Immune-Mediated Medical Conditions
PIP	Paediatric Investigation Plan
PP-EFF	Per-protocol efficacy
PP-IMM	Per-protocol immunogenicity
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic safety update report
PY	Patient year(s)
RBD	Receptor-binding domain
RMP	Risk management plan
RNA	Ribonucleic acid
RR	Relative risk
rRNA	Ribosomal ribonucleic acid
rS	Recombinant Spike protein
RSI	Request for supplementary information
RT-PCR	Reverse transcription polymerase chain reaction
S	Spike (protein)
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SARS-CoV-2 rS	SARS-CoV-2 recombinant spike protein nanoparticle vaccine
SCR	Seroconversion rate
SmPC	Summary of Product Characteristics
SOC	System organ class
SpO_2	Peripheral capillary oxygen saturation
TEAE	Treatment-emergent adverse event
ULOQ	Upper limit of quantification
VE	Vaccine efficacy / effectiveness
VOC	Variant(s) of concern
VOI	Variant(s) of interest
WHO	World Health Organisation

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novavax CZ, a.s. submitted to the European Medicines Agency on 29 March 2022 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include use in adolescents 12 to 17 years of age for Nuvaxovid, based on data from study 2019nCoV-301, a Phase 3, Randomized, Observer-Blinded, Placebo-Controlled Study to evaluate the efficacy, safety, and immunogenicity of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine (SARS-CoV-2 rS) with Matrix-M Adjuvant in Adult Participants ≥ 18 Years with a Pediatric Expansion in Adolescents (12 to < 18 Years); as a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 1.1 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0126/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0126/2021 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Thalia Marie Estrup Blicher

Timetable	Actual dates
Submission date	29 March 2022
Start of procedure:	20 April 2022
PRAC Rapporteur Assessment Report	25 April 2022
PRAC members comments	27 April 2022
CHMP Rapporteur Assessment Report	28 April 2022
PRAC Outcome	5 May 2022
CHMP members comments	6 May 2022
Updated CHMP Rapporteur Assessment Report	11 May 2022
Request for supplementary information (RSI)	19 May 2022
CHMP Rapporteur Assessment Report	3 June 2022
PRAC Rapporteur Assessment Report	3 June 2022
CHMP members comments	13 June 2022
ETF meeting	14 June 2022
Updated CHMP Rapporteur Assessment Report	16 June 2022
Opinion	23 June 2022

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

End of December 2019, the World Health Organization (WHO) was informed about a cluster of cases of viral pneumonia of unknown cause in Wuhan, China. In mid-January 2020 the pathogen causing this atypical pneumonia was identified as a novel coronavirus, severe acute respiratory coronavirus 2 (SARS-CoV-2) and genome sequence data were published. Since then, the virus has spread globally and on 30 January 2020 the WHO declared the outbreak a Public Health Emergency of International Concern and on 11 March 2020 a pandemic. The pandemic is ongoing despite unprecedented efforts to control the outbreak. According to ECDC, histologic findings from the lungs include diffuse alveolar damage similar to lung injury caused by other respiratory viruses, such as MERS-CoV and influenza virus. A distinctive characteristic of SARS-CoV-2 infection is vascular damage, with severe endothelial injury, widespread thrombosis, microangiopathy and angiogenesis.

State the claimed the therapeutic indication

The proposed indication and dosing administration for Nuvaxovid are:

- **Proposed indication:** Nuvaxovid is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older (extension including 12 to <18 year olds)
- **Dosing administration:** 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 of the SmPC).

Epidemiology and risk factors

The majority of SARS-CoV-2 infections result in asymptomatic or mild disease with full recovery. Underlying health conditions such as hypertension, diabetes, cardiovascular disease, chronic respiratory disease, chronic kidney disease, immune compromised status, cancer and obesity are considered risk factors for developing severe COVID-19. Other risk factors include organ transplantation and chromosomal abnormalities. Increasing age is another risk factor for severe disease and death due to COVID-19. COVID-19 in adolescents is mostly a mild disease although severe cases also occur rarely.

Following worldwide spread of the original SARS-CoV-2 strain, more numerous variants have emerged with several variants characterised as Variants of Concern and being dominant in circulation at different times: the B.1.1.7 (Alpha), P.1 (Gamma), B.1.351 (Beta), B.1.617.2 (Delta), and B.1.1.529 (Omicron) variants of SARS CoV-2, respectively, with confirmed acquisition of mutations in key antigenic sites in the receptor-binding domain (RBD) and N-terminal domain of the S protein. At present, the Omicron variant is the dominant circulating variant in Europe. Omicron was listed as a VOC by the WHO on 26 November 2021; it has at least 30 amino acid substitutions in the SARS-CoV-2 S protein, including 15 in the RBD, that suggest this variant will also be associated with significant reductions in neutralising activity by vaccine sera.

Aetiology and pathogenesis

SARS-CoV-2 is a positive-sense single-stranded RNA (+ssRNA) virus, with a single linear RNA segment. SARS-CoV-2 has four structural proteins, known as the S (spike), E (envelope), M (membrane), and N (nucleocapsid) proteins. The spike protein contains a polybasic cleavage site, a characteristic known to increase pathogenicity and transmissibility in other viruses. The spike is responsible for allowing the virus to attach to and fuse with the membrane of a host cell, and is considered a relevant antigen for vaccine development because it was shown that antibodies directed against it neutralise the virus and it elicits an immune response that prevents infection in animals.

Transmission occurs primarily via respiratory droplets from coughs and sneezes and through aerosols. The median incubation period after infection to the development of symptoms is four to five days. Most symptomatic individuals experience symptoms within two to seven days after exposure, and almost all symptomatic individuals will experience one or more symptoms before day twelve. Common symptoms include fever, cough, fatigue, breathing difficulties, and loss of smell and taste and symptoms may change over time. The major complication of severe COVID-19 is acute respiratory distress syndrome (ARDS) presenting with dyspnoea and acute respiratory failure that requires mechanical ventilation. In addition to respiratory sequelae, severe COVID-19 has been linked to cardiovascular sequelae, such as myocardial injury, arrhythmias, cardiomyopathy and heart failure, acute kidney injury often requiring

renal replacement therapy, neurological complications such as encephalopathy, and acute ischemic stroke.

Clinical presentation, diagnosis

The severity of COVID-19 varies. The disease may take a mild course with few or no symptoms, resembling other common upper respiratory diseases such as the common cold. Mild cases typically recover within two weeks, while those with severe or critical diseases may take three to six weeks to recover.

The US Centers for Disease Control and Prevention (CDC) defined COVID 19 symptoms as including 1 or more of the following:

- Fever
- New or increased cough
- New or increased shortness of breath
- Chills
- New or increased muscle pain
- New loss of taste or smell
- Sore throat
- Diarrhoea
- Vomiting
- Fatigue
- Headache
- Nasal congestion or runny nose
- Nausea

Among those who have died, the time from symptom onset to death has ranged from two to eight weeks. Prolonged prothrombin time and elevated C-reactive protein levels on admission to the hospital are associated with severe course of COVID-19 and with a transfer to ICU.

The gold standard method of testing for presence of SARS-CoV-2 is the reverse transcription polymerase chain reaction (RT-PCR), which detects the presence of viral RNA fragments. As this test detects RNA but not infectious virus, its ability to determine duration of infectivity of patients is limited. The test is typically done on respiratory samples obtained by a nasopharyngeal swab, a nasal swab or sputum sample.

Management

The management of COVID-19 cases has developed during 2020, and includes supportive care, which may include fluid therapy, oxygen support, and supporting other affected vital organs. Treatment of hospitalised patients encompass anti-inflammatory agents such as dexamethasone and statins, targeted immunomodulatory agents and anticoagulants as well as antiviral therapy (e.g. remdesivir, monoclonal antibodies).

These therapies have shown variable and limited impact on the severity and duration of illness, with different efficacies depending on the stage of illness and manifestations of disease. While care for individuals with COVID-19 has improved with clinical experience, there remains an urgent and unmet medical need for vaccines able to prevent or mitigate COVID-19 infections during the ongoing pandemic. Especially protection of vulnerable groups and mitigating the effects of the pandemic on a population level are desired.

2.1.2. About the product

Nuvaxovid (also referred to in this report as NVX-CoV2373) is a vaccine developed for prevention of COVID-19 caused by SARS-CoV-2.

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.

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.

The intended indication for Nuvaxovid is 'for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older'.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The MAH has not applied for CHMP scientific advice on the paediatric development of Nuvaxovid. A PIP has been agreed (PIP P/0126/2021) and the current study is part of the PIP.

2.1.4. General comments on compliance with GCP

The MAH states that all clinical studies were performed in accordance with GCP. The submitted study, 2019nCoV-301, was also included in the application for initial approval. The trial has been expanded to include adolescents aged 12 to <18 years.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

Furthermore, the MAH has provided a statement to the effect that all clinical trials conducted outside the European Union were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

The clinical development program for SARS-CoV-2 rS with Matrix-M adjuvant in adolescent participants 12 to < 18 years of age comprises the ongoing paediatric expansion of Clinical Study 2019nCoV-301:

Table 1. Ongoing MAH-Sponsored Clinical Study of SARS-CoV-2 rS Vaccine with Matrix-M Adjuvant in Adolescent Participants 12 to < 18 Years of Age Across the SARS-CoV-2 rS Vaccine Clinical Development Programme

Clinical Study Number (Country)	Study Design	Primary Endpoints	Dosage, Duration and Dosage Regimen	Planned (Treated) Number of Subjects	Study Status[1]	Cross-References
2019nCoV-301 (US)	A Phase 3, randomized, observer-blinded, placebo-controlled study to evaluate the efficacy, safety, and immunogenicity of SARS-CoV-2 rS with Matrix-M adjuvant in adult participants ≥ 18 years of age with a pediatric expansion (12 to < 18 years of age). Includes a blinded crossover vaccination period for pediatric participants initiated after following collection of sufficient safety data to support an Application for Emergency Use Authorization (EUA).[2] In the Crossover Vaccination Period, participants will receive the alternate trial vaccine or placebo than received in the Initial Set of Vaccinations.[3]	Effectiveness Efficacy Immunogenicity Safety	Initial Set of Vaccinations 5 µg SARS-CoV-2 rS + 50 µg Matrix-M adjuvant or Placebo Crossover Set of Vaccinations 5 µg SARS-CoV-2 rS + 50 µg Matrix-M adjuvant or Placebo IM injection on Days 0 and 21 (+ 7 days) of Initial and Crossover Vaccination Periods; antigen and adjuvant were administered as a co-formulation	Total: 3,000 (2,232) SARS-CoV-2 rS: 2,000 (1,487) Placebo: 1,000 (745)	Ongoing (enrollment, initial, and crossover vaccination complete[3]	Protocol (Version 10.0 – dated 11 Oct 2021) Statistical analysis plan (Version 4.0 – dated 01 Oct 2021)

Abbreviations: COVID-19 = coronavirus disease 2019; FDA = United States Food and Drug Administration; HIV = human immunodeficiency virus; IM = intramuscular; SARS-CoV-2 rS = severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine; UK = United Kingdom; US = United States.

1. Study status as of 01 February 2022.
2. FDA Guidance for Industry: Emergency Use Authorization for Vaccines to Prevent COVID-19 (25 May 2021).
3. Data for the blinded crossover portion of Clinical Study 2019nCoV-301 in adolescents 12 to < 18 years of age are not included in this submission.

2.3.2. Pharmacodynamics

Immunogenicity results are presented together with the efficacy analysis.

A summary of immunogenicity, clinical virology and diagnostic assays used in the adolescent study is given in the table below. All the immunogenicity assays shown in the table are based on the index SARS-CoV-2 strain from the start of the COVID-19 pandemic in December 2019 (Wu 2020), on which the SARS-CoV-2 rS (BV2373) spike protein vaccine antigen is also based.

All assays have been used consistently through the clinical development programme, and are known to provide credible and reliable results. All assays have been formally validated, and the assays were assessed in detail for the application for conditional marketing authorisation (CMA) for NVX-CoV2373 use in individuals > 18 years of age.

Thus, the in vitro immunogenicity assays employed in the adolescent study are fit for purpose and raise no concerns.

Table 2. Summary of immunogenicity, clinical virology and diagnostic assays employed in the paediatric study.

Assay	Laboratory	Status	Cross-references for analytical methodology
Immunogenicity			
Anti-S protein Binding IgG ELISA	Novavax Clinical Immunology 21 Firstfield Road Gaithersburg, MD 20878 USA	Validated	QAG_04556: Novavax Clinical Immunology Validation Report
Wild-type virus neutralization	360biolabs Burnet Institute 85 Commercial Road Melbourne, Australia 3004	Validated	360bl-VR_NOVA-05_MN_v02
hACE2 Receptor Binding Inhibition ELISA	Novavax Clinical Immunology (Gaithersburg, Maryland, US)	Validated	QAG_04394 QAG_05890 CL_5.3.1.4_002761
Clinical virology			
SARS-CoV-2 whole-genome sequencing	University of Washington Seattle, Washington		VIRO_1800-3100 Swift SNAP for SARS-CoV-2 Whole Genome Sequencing (WGS) Manual Sciclone NGS Workstation
Diagnostic assays			
Anti-Nucleocapsid	University of Washington Seattle, Washington	Validated	Roche Elecsys Package Insert VIRO-1000-281: Roche Elecsys Anti-SARS-CoV-2 (utilizing e411, SN 87Z516)-Validation Summary)
SARS-CoV-2 RT-PCR	University of Washington Seattle, Washington	Validated	Abbott RealTi*me* SARS-CoV-2 Abbott RealTime Quantitative SARS-CoV-2 Assay (VIRO_1000-255) Assay Package Insert Validation Report (VIRO_1000-261, Version 1.0): Extended Stability of Dry Swab Collections at Room Temperature and Refrigerated (2-8°C) for SARS-CoV-2 EUA Validation Summary (VIRO_1000-264, Version 1.0): Extended Stability of ISwab+ Collections at Ambient and Refrigerator Conditions for SARS-CoV-2 EUA Validation Summary (VIRO_1000-277, Version 1.0): Abbott RealTime Quantitative SARS-CoV-2 Assay Utilizing the NJB#2 m2000 System Degli-Angeli et al, 2020. Skalina et al, 2020.

2.4. Clinical efficacy

2.4.1. Main study

Study 2019nCoV-301, a phase 3, randomised, placebo controlled study to evaluate the efficacy, safety and immunogenicity of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine (SARS-CoV-2 rS) with Matrix M1 adjuvant in adult participants ≥ 18 years with a paediatric expansion in adolescents (12 to <18 years).

Methods

Study participants

The paediatric expansion enrolled healthy or medically stable adolescent participants 12 to < 18 years of age without a history of previous laboratory confirmed diagnosis of SARS-CoV-2 infection / COVID-19. Persons with clinically significant immunosuppression, who were breastfeeding, pregnant or who were planning to become pregnant were excluded from participation.

Treatments

Participants received 2 intramuscular (IM) 0.5 mL injections of SARS-CoV-2 rS (5 µg) + Matrix-M1 adjuvant (50 µg) (NVX-CoV2373) or placebo (normal saline) on D0 and D21. Following the accrual of 2 months safety data, participants were offered the alternative vaccine/placebo in a blinded fashion.

Objectives

The following **primary objectives** were determined for the paediatric expansion:

- To evaluate the efficacy of a 2-dose regimen of SARS-CoV-2 rS adjuvanted with Matrix-M1 compared to placebo against PCR-confirmed symptomatic COVID-19 illness diagnosed ≥ 7 days after completion of the second injection in the initial set of vaccinations of adolescent participants 12 to < 18 years of age.
- To describe the safety experience for the vaccine versus placebo in adolescent participants (12 to < 18 years of age) based on solicited short-term reactogenicity by toxicity grade for 7 days following each vaccination (Days 0 and 21) after the initial set of vaccinations.
- To assess overall safety through 49 days (28 days after second injection of each set of vaccinations [initial and crossover]) by comparing vaccine versus placebo for all unsolicited AEs and MAAEs.
- To assess the frequency and severity of MAAEs attributed to vaccine, AESIs, or SAEs through the EoS and to compare vaccine versus placebo after each set of vaccinations (initial and crossover).
- To assess all-cause mortality in vaccine versus placebo recipients after each set of vaccinations (initial and crossover).
- To assess non-inferiority of the neutralising antibody response for all adolescent participants seronegative to anti-SARS-CoV-2 NP antibodies at baseline, compared with that observed in seronegative adult participants 18 to < 26 years of age from the Adult Main Study (Immunogenicity Population participants before crossover).

Secondary objectives were:

- To evaluate the efficacy of a 2-dose regimen of SARS-CoV-2 rS adjuvanted with Matrix-M1 compared to placebo against PCR-confirmed symptomatic COVID-19 illness due to SARS-CoV-2 variant not considered as a "variant of concern /interest" according to the CDC Variants Classification, diagnosed ≥ 7 days after completion of the second injection in the initial set of vaccinations of adolescent participants 12 to < 18 years of age.
- To evaluate the efficacy of a 2-dose regimen of SARS-CoV-2 rS adjuvanted with Matrix-M1 compared to placebo against PCR-confirmed moderate-to-severely symptomatic COVID-19 illness diagnosed ≥ 7

days after completion of the second vaccination in the initial set of vaccinations of adolescent participants 12 to < 18 years of age.

- To assess VE against ANY symptomatic SARS-CoV-2 infection.
- To assess VE according to race and ethnicity.
- To assess the durability of VE (measured by all defined efficacy endpoints) in adolescents after initial active vaccine recipients versus crossover (delayed) active vaccine recipients.
- To monitor occurrence and severity of COVID-19 cases by following participant-reported symptoms.
- To assess the neutralising antibody response to SARS-CoV-2 for adolescent participants by subsets with and without anti-NP antibodies at baseline, compared with that observed in adult participants 18 to < 26 years of age from the Adult Main Study (Immunogenicity Population participants before crossover).
- To assess the anti-spike IgG antibody response and hACE2 inhibiting antibody response at Day 35 for adolescent participants by subsets with and without detectable anti-NP antibodies at baseline, compared with that observed in adult participants 18 to < 26 years of age from the Adult Main Study (Immunogenicity Population participants before crossover).

Exploratory objectives were:

- To evaluate the efficacy of study vaccine compared to placebo against PCR-confirmed symptomatic COVID-19 illness due to a SARS-CoV-2 variant considered as a "variant of concern / interest" according to the CDC Variants Classification, diagnosed ≥ 7 days after completion of the second vaccination in the initial set of vaccinations of adolescent participants 12 to < 18 years of age.

Outcomes/endpoints

Primary endpoints:

First episode of PCR-positive mild, moderate, or severe COVID-19, where severity is defined as:

Mild COVID-19 (≥ 1 of the following):

- Fever (defined by subjective or objective measure, regardless of use of anti-pyretic medications)
- New onset cough
- ≥ 2 additional COVID-19 symptoms:
  - New onset or worsening of shortness of breath or difficulty breathing compared to baseline.
  - New onset fatigue.
  - New onset generalised muscle or body aches.
  - New onset headache.
  - New loss of taste or smell.
  - Acute onset of sore throat, congestion, or runny nose.
  - New onset nausea, vomiting, or diarrhoea.

OR Moderate COVID-19 (≥ 1 of the following):

- High fever (≥ 38.4°C) for ≥ 3 days (regardless of use of anti-pyretic medications, need not be contiguous days).
- Any evidence of significant LRTI:
  - Shortness of breath (or breathlessness or difficulty breathing) with or without exertion (greater than baseline).
  - Tachypnoea: 24 to 29 breaths per minute at rest.

    - SpO_2: 94% to 95% on room air.
    - Abnormal chest X-ray or chest CT consistent with pneumonia or LRTI.
- Adventitious sounds on lung auscultation (eg, crackles/rales, wheeze, rhonchi, pleural rub, stridor).

OR Severe COVID-19 (≥ 1 of the following):

- Tachypnoea: ≥ 30 breaths per minute at rest.
- Resting heart rate ≥ 125 beats per minute.
- SpO_2: ≤ 93% on room air or PaO_2/FiO_2 < 300 mmHg.
- High flow oxygen (O_2) therapy or NIV/NIPPV (e.g., CPAP or BiPAP).
- Mechanical ventilation or ECMO.
- One or more major organ system dysfunction or failure to be defined by diagnostic testing/clinical syndrome/interventions, including any of the following:
    - Acute respiratory failure, including ARDS.
    - Acute renal failure.
    - Acute hepatic failure.
    - Acute right or left heart failure.
    - Septic or cardiogenic shock (with shock defined as SBP < 90 mm Hg OR DBP < 60 mm Hg).
    - Acute stroke (ischemic or haemorrhagic).
    - Acute thrombotic event: AMI, DVT, PE.
    - Requirement for: vasopressors, systemic corticosteroids, or haemodialysis.
- MIS-C, as per the CDC definition:
    - An individual aged < 21 years presenting with fever (> 38.0°C for ≥ 24 hours, or report of subjective fever lasting ≥ 24 hours), laboratory evidence of inflammation (including, but not limited to, one or more of the following: an elevated CRP, ESR, fibrinogen, procalcitonin, d-dimer, ferritin, LDH, or IL-6, elevated neutrophils, reduced lymphocytes and low albumin), and evidence of clinically severe illness requiring hospitalisation, with multisystem (> 2) organ involvement (cardiac, renal, respiratory, hematologic, Gastrointestinal, dermatologic or neurological); AND
    - No alternative plausible diagnoses; AND
    - Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms.
- Admission to an ICU.
- Death

Endpoint collection methods

Starting on Day 4, throughout the first 12 months of the study, parent(s)/caregiver(s) of participants were asked to report symptoms of COVID-19 (see Table 3 for symptoms suggestive of COVID-19) to the site as soon as possible after symptoms onset, or during the weekly remote contact. Fever and other symptoms of COVID-19 (including date of onset, duration, etc.) were collected in a paper memory aid and were reported to the sites by the parent(s)/caregiver(s) either as a spontaneous phone call or during the weekly remote contact during the first 12 months. If the parent(s)/caregiver(s) report symptoms compatible with COVID-19 by spontaneous contact or during the weekly contact, the study site then scheduled an in-person Acute Illness Visit.

Table 3. Symptoms suggestive of COVID-19

- Fever (body temperature > 38.0° C, in the absence of other symptoms) or chills
- New onset or worsening of cough compared with baseline
- New onset or worsening of shortness of breath or difficulty breathing over baseline
- New onset fatigue
- New onset generalized muscle or body aches
- New onset headache
- New loss of taste or smell
- Acute onset sore throat
- Acute onset congestion or runny nose
- New onset nausea or vomiting
- New onset of diarrhea

Abbreviations: COVID-19 = coronavirus disease 2019.

At the in-person Acute Illness Visit, participants were queried regarding AE symptoms, concomitant medications taken for these symptoms, underwent a targeted physical examination (to include oxygen [O_2] saturation and respiratory rate), as indicated by participant's signs and symptoms, and obtained by the study personnel a medically attended nasal swab, and a blood sample for serologic testing. Medically attended swabs collected at the Acute Illness Visit were processed at the study site for shipment to the central laboratory according to established procedures as described in the Laboratory Manual.

All Acute Illness Visits and assessments performed during the visits were recorded in the participant's electronic case report form (eCRF). Study participants that had medically attended nasal swabs were confirmed at the central laboratory to be PCR-positive for SARS-CoV-2 at the Acute Illness Visit were contacted by the study site to arrange a Convalescent Visit. The Convalescent Visit was to occur approximately 1 month (or as soon thereafter, as feasible) after the onset of the PCR-confirmed case of COVID-19 at the Acute Illness Visit to assess status of AEs, record the clinical course of the disease on the Endpoint Form, and obtain a blood sample for convalescent serologic testing.

Nasal swabs of the anterior nares were obtained at the study site on Day 0 (prior to study vaccination), at the Acute Illness Visit, and at the first crossover vaccination visit. There was no self-swab collection in the adolescent participants.

Immunogenicity Endpoint:

- Neutralising antibody response at Day 35 for all adolescent participants seronegative to anti-SARS-CoV-2 NP antibodies at baseline, compared with that observed in seronegative adult participants 18 to < 26 years of age from the Adult Main Study (Immunogenicity Population participants before crossover).

Immunogenicity assessments

The primary immunogenicity endpoint was determined with a validated wild-type virus microneutralisation assay. There are 7 scheduled blood draws for immunogenicity assessments at the Day 0, 21, 35, C1 (Day 180), and Months 12, 18, and 24 visits, and during visits (acute illness / convalescent /general). For participants in the CMI cohort only (n = ~50), additional blood was collected to obtain PBMCs at the Day 0, 7, and 28 visits.

Secondary Endpoints:

- First episode of PCR-positive COVID-19, as defined under the primary endpoint, shown by gene sequencing to represent a variant not considered as a "variant of concern / interest" according to the CDC Variants Classification.
- First episode of PCR-positive moderate or severe COVID-19, as defined under the primary endpoint.

- ANY symptomatic SARS-CoV-2 infection, defined as: PCR-positive nasal swab and ≥ 1 of any of the symptoms in Table 3.
- Proportion of adolescent participants reporting SARS-CoV-2 infection (COVID-19) from Day 28 through end of Year 1, with severity classification as defined in the Adult Main Study (mild, moderate, or severe).
- Neutralising antibody response at Day 35 for adolescent participants by age strata and with and without anti-SARS-CoV-2 NP antibodies at baseline, compared with that observed in adult participants 18 to < 26 years of age from the Adult Main Study (Immunogenicity Population participants before crossover).
- Antibodies to SARS-CoV-2 NP at Days 0 and 35, and at Months 12, 18 and 24 will be used to determine natural infection and to determine the incidence of undiagnosed infection acquired during study follow-up.
- Serum IgG levels to SARS-CoV-2 S protein, hACE2 inhibition titers 14 days after second injection of the initial vaccination series (Day 35) in adolescent participants and subsets with and without anti-NP antibodies at baseline.
- Description of course, treatment and severity of COVID-19 reported after a PCR-confirmed case via the Endpoint Form.

Exploratory Endpoints:

- First episode of PCR-positive COVID-19, as defined under the primary endpoint, shown by gene sequencing to represent a "variant of concern / interest" according to the CDC Variants Classification.

Sample size

The sample size for the paediatric expansion was chosen to provide an adequate safety database of ≥ 2,000 paediatric recipients of investigational product to support licensure of NVX-CoV2373 in adolescent participants 12 to < 18 years of age. With 2,000 participants in the active vaccine group, there is a >90% probability of observing at least 1 participant with an AE if the true incidence of the AE is 0.12% and a 99% probability if the true incidence of the AE is 0.23%. Recruitment of study participants intended to attempt to enrol a similar number of adolescent participants in the 12 to < 15 and 15 to < 18 year old age groups.

The analysis of efficacy in the paediatric expansion was descriptive in nature using the same methods as the adult part of the study but with no formal statistical hypothesis tested.

A non-randomised non-inferiority (NI) analysis of immunogenicity (neutralising antibodies) was performed using a random sample of 750 adult participants aged 18 to < 26 years of age from the adult part of the study to provide approximately 400 adult participants for the NI analysis, accounting for the 2:1 randomisation and 500 adult participants accounting for 20% non-evaluability. Similarly, 750 adolescent participants were randomly selected from the paediatric expansion for testing of neutralisation titers, which provided approximately 400 adolescent participants for the NI analysis, accounting for the 2:1 randomisation and 20% non-evaluability.

Assuming a standard deviation of log10 neutralisation antibody titer of 0.6, there was over 85% power (through simulations) to demonstrate the first 2 NI criteria when assuming an underlying GMT for the 18 to < 26 years of age group up to 1.1-fold higher than the 12 to < 18 years of age group.

With seroconversion (SCR) defined as ≥ 4-fold increase in neutralisation titers (MN50) at Day 35 relative to baseline titres, and assumed SCRs of 95% in the 18 to < 26 years of age group, there was over 80% power to demonstrate the third NI criterion for a difference as large as 4% lower in the 12 to < 18 years of age group. A descriptive assessment of immunogenicity evaluated the same criteria in the 12 to < 15 and 15 to < 18 years of age groups separately.

Unlike neutralising antibody responses that were only assessed in a subset of adolescent participants, anti-S IgG antibody responses and hACE2 receptor binding inhibition antibody responses were assessed in the totality of the adolescent participants that were part of the PP-IMM (per-protocol immunogenicity) population and PP-IMM-2 population (which includes all participants regardless of sero- and PCR-status at baseline) (see statistical methods section below).

Randomisation

Participants were randomised to study treatment in a 2:1 ratio via block randomisation according to a list produced by the biostatistics CRO. As block size is considered potentially unblinding information, it will be known to the Study Biostatistician only. An IWRS will be responsible for the allocation of randomisation numbers to individual participants. No stratification by site was conducted, however, at the time of randomisation of a participant at a site, a full block will be assigned to the site in order to maintain treatment assignment balance in the planned ratio at each site and allow for site and region effects to be assessed. Efforts were made to enrol similar numbers of participants in the subgroups 12 to < 15 years of age, and 15 to < 18 years of age.

The non-inferiority analysis comprised a non-randomised comparison.

Enrolment of the full adolescent cohort of participants (12 to < 18 years) will be contingent upon the review of early safety data (i.e., 7 days of reactogenicity and overall safety post-dose 1) to be reviewed in the first ~60 enrolled adolescents (randomised in a 2:1 ratio to receive 5 µg SARS-CoV-2 rS adjuvanted with 50 µg Matrix-M1 or placebo) before enrolment of the remainder of the adolescent participants (N=~2,940). Likewise, administration receipt of the second vaccine dose to the full participant population will be contingent upon the review of early safety data (i.e., 7 days of reactogenicity and overall safety post-dose 2) in the first ~60 enrolled adolescents before dosing the remainder of the adolescent participants.

Blinding (masking)

This is an observer-blinded study. To maintain the blind, placebo vaccination via IM route will be included and unblinded study site personnel will manage vaccine logistics, preparation, and administration according to the Pharmacy Manual so as to maintain the blind from the remainder of the study site personnel and participants. The unblinded study site personnel may administer study vaccine if qualified to do so, but will not be involved in study-related assessments or have participant contact for data collection after administration of trial vaccine. At the time of implementation of the blinded crossover period, a similar procedure will be employed to ensure that all study participants and personnel remain blinded as to initial and subsequent treatment assignment.

Statistical methods

There were 7 main analysis sets used in this trial:

• The Intent-to-Treat (ITT) Analysis Set included all participants who were randomised, regardless of protocol violations or missing data. The ITT analysis set was used for participant disposition summaries and was analysed according to the treatment arm to which the participant was randomised.

• The Full Analysis Set (FAS) included all participants who were randomised and received at least 1 dose of study vaccine/placebo, regardless of protocol violations or missing data. Participants who were unblinded with an intention to receive other COVID-19 vaccines were censored at the time of unblinding. The FAS population was analysed according to the treatment group to which participants were randomised. The FAS analysis sets were used for supportive analyses. When the efficacy endpoints were analysed using FAS, baseline SARS-CoV-2 seropositivity or nasal swab PCR-positivity was ignored.

• The Safety Analysis Set included all participants who received at least 1 dose of study vaccine/placebo. Participants in the Safety Analysis Set were analysed according to the treatment actually received. In cases where information is available that indicated that a participant received both active and placebo vaccine during the initial period, the participant was analysed as part of the active group.

• The Per-Protocol Efficacy (PP-EFF) Analysis Set included all participants who received the full prescribed regimen of trial vaccine and had no major protocol deviations that occurred before the first COVID-19 positive episode (i.e., participant was censored at the time of the protocol deviation) and were determined to affect the efficacy outcomes, including baseline SARS-CoV-2 seropositivity or nasal swab PCR-positivity. Participants who were unblinded with an intention to receive other COVID-19 vaccines were censored at the time of unblinding. Although the study enrolled participants regardless of SARS-CoV-2 serologic status at the time of initial vaccination, any participants with confirmed infection or prior infection due to SARS-CoV-2 at baseline, by nasal swab PCR or serology, were excluded from the PP-EFF population. PP-EFF was the primary set for all efficacy endpoints. Participants determined to have positive nasal swab PCR or serology immediately prior to the first crossover vaccination will be excluded from the post-crossover PP-EFF population.

• A second PP-EFF (PP-EFF-2) Analysis Set was defined to allow for evaluation of baseline serostatus analysis' impact on VE. The PP-EFF-2 Analysis Set followed the same method described in the PP-EFF population with the exception that it included all participants regardless of baseline serostatus (based on anti-NP). The analysis of VE using this population was dependent on whether there existed an endpoint event for the relevant analysis in a participant who had a baseline positive anti-NP result.

• The Per Protocol Immunogenicity (PP-IMM) Analysis Set was determined for each study visit and may be assay specific (i.e., serum vs PBMC, and within serum IgG, MN, hACE2). The PP-IMM Analysis Set included participants that had at least a baseline and 1 serum sample result available after vaccination and had no major protocol violations that were considered clinically relevant to impact immunological measures prior to the visit in question. The PP-IMM Analysis Set also excluded participants who had a PCR positive nasal swab between baseline up to the visit analysed. All participants in the PP-IMM analysis population were designated at time of vaccination within the immunogenicity subset. For participant visits on or after Day 21, participants had to receive the second vaccination to be included in the PP-IMM Analysis Set. Durability of immune responses will be evaluated in participants who provided serologic data at Months 12, 18, and 24, taking into account when they received active vaccine and if/when they were infected with SARS-CoV-2, based on PCR or serology.

• A second Per Protocol Immunogenicity (PP-IMM-2) Analysis Set was defined to allow for evaluation of baseline serostatus analysis's impact on immune response. The PP-IMM-2 Analysis Set followed the same method described in the PP-IMM population with the exception that it included prior exposed participants determined using baseline SARS-CoV-2 nasal swab or seropositivity at screening to assess if immune responses differed between previously exposed and unexposed individuals.

The review and determination for exclusion from the PP-EFF, PP-EFF-2, PP-IMM, and PP-IMM-2 Analysis Sets were carried out in a blinded fashion prior to unblinding for the analysis.

General Statistical Conventions

Unless otherwise stated, all statistical testing was two-sided and was performed using a significance (alpha) of 0.05 However, as the study was set up being descriptive, these p-values are of limited relevance. Two-sided 95% CIs were provided when relevant.

Immunology data consisting of ELISA unit (EU) and titer data were summarised using geometric means, also known as geometric mean EUs/titers (GMEU/GMT), geometric mean fold rise (GMFR) and seroconversion rate (SCR). Immunology results below the lower limit of quantification (LLOQ) were summarised and reported using 0.5 × LLOQ. Immunology results above the upper limit of quantification (ULOQ) were summarised and reported using the ULOQ. For categorical variables, summaries included counts of participants and percentages. CIs surrounding proportions may be constructed using a normal approximation for larger samples and exact methods for smaller samples, whichever was appropriate for the data. The two-sided 95% CI on this difference of seroresponse rates will be computed based on the method of Miettinen and Nurminen.

The paediatric expansion part of this study was not adjusted for multiplicity.

Subgroup analyses were conducted to determine if there was a difference in efficacy and safety of the vaccine by age group (12 to < 15 years of age, 15 to < 18 years of age), gender, race, and ethnicity. These analyses may be conducted in the efficacy, immunogenicity, and safety analysis sets as appropriate for the type of analysis being conducted.

All analyses were descriptive.

Primary Efficacy analyses

The VE was defined as VE (%) = (1 − RR) × 100, where RR = relative risk of incidence rates between the 2 trial vaccine groups (NVX-CoV2373/placebo). The RR was estimated by exponentiating the treatment group coefficient from a Poisson regression analysis with robust error variance [Zou 2004]. A Poisson regression model utilising robust error variance and an offset to account for variable follow-up time was used to estimate the RR and VE. A two-sided CI around the estimate also provided the Maximum Likelihood Estimator (MLE) 95% CI around the VE. Due to the potential for sparse numbers of cases among potential covariates, some covariates were not considered in the model.

Provided that the Poisson model converges, a Cox proportional hazard (CPH) model using the same dependent and explanatory variables was developed as a supportive analysis.

In the case where there were zero endpoints for one of the vaccine groups or the total number of endpoints in both treatment groups combined was less than 5, a Poisson model was substituted with an exact conditional binomial method.

The primary analysis was conducted in the PP-EFF and FAS analysis sets. Additionally, the primary efficacy endpoint may be evaluated in the PP-EFF-2 population among the seropositive and seronegative participants.

Primary Immunogenicity analyses

A formal non-randomised NI analysis of the primary effectiveness endpoint, neutralising antibody to SARS-CoV-2 at Day 35, was carried out using the PP-IMM analysis set. The NI analysis of adolescent participants compared with the 18 to < 26 year old immunogenicity cohort from the adult part of the study was performed using the point estimate and upper bound of the two-sided 95% CI on the ratio of

GMTs between 2 age cohorts (adults 18 to < 26 year old cohort in the adult part of the study/adolescent cohort in the paediatric extension) against the prespecified success criteria. The ratio of GMTs between the 2 age cohorts and the corresponding two-sided 95% CI were calculated on log-transformed titers using the analysis of covariance (ANCOVA) with age cohort and baseline (Day 0) measurement as the covariate. In addition, the difference of SCRs between the 2 age cohorts was computed using a definition of seroconversion as 4-fold rise in neutralisation titers at Day 35 relative to Day 0. The two-sided 95% CI on this difference of SCRs was computed based on the method of Miettinen and Nurminen.

Successful demonstration of NI (primary immunogenicity objective) required meeting the following 3 pre-specified criteria simultaneously:

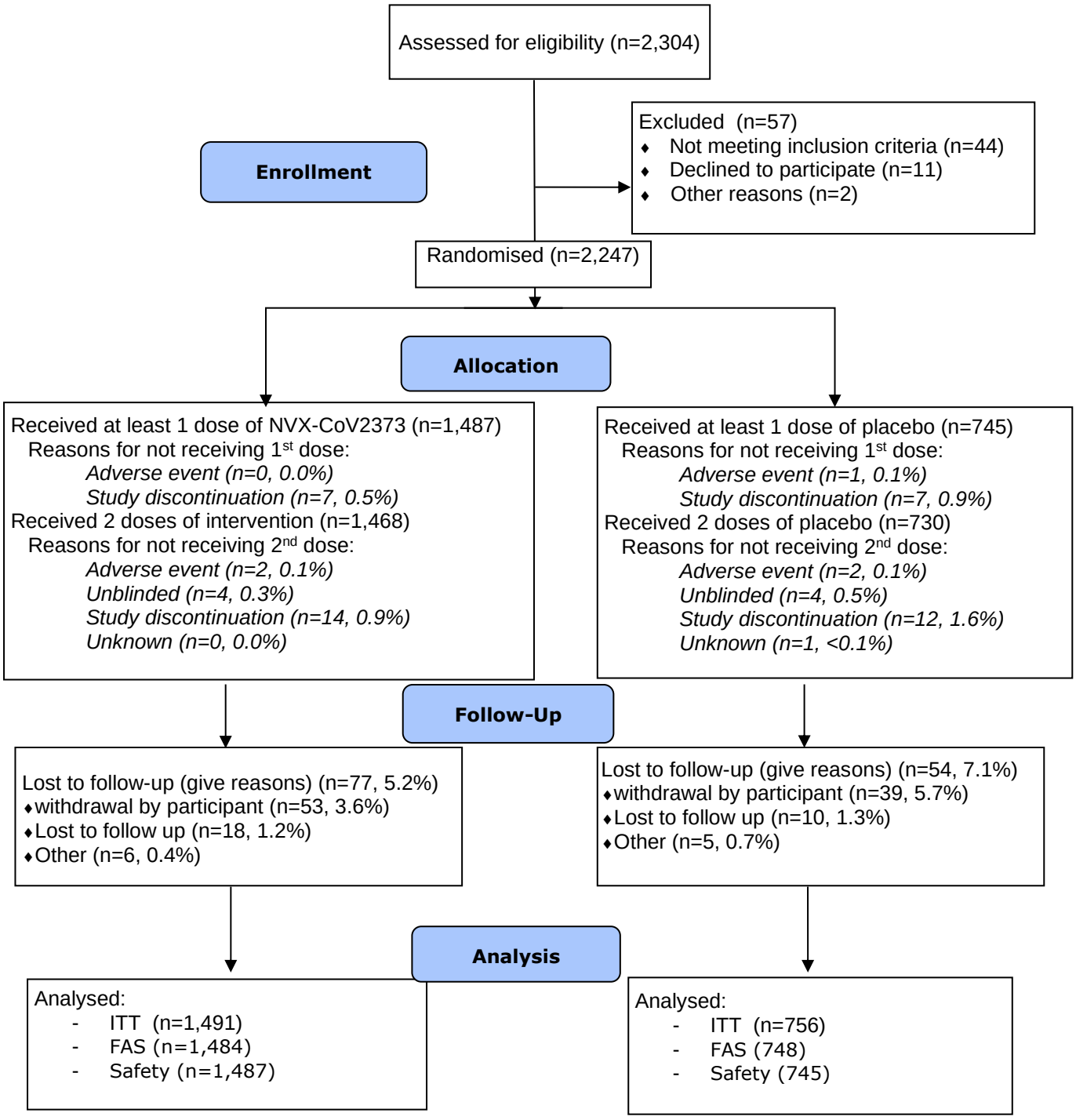
1. Upper bound of two-sided 95% confidence interval (CI) for the ratio of geometric mean titers (GMTs) (GMT18-< 26yo /GMT12-<18yo) < 1.5

2. Point estimate of the ratio of GMTs ≤ 1.22 (estimated as square root of 1.5)

3. Upper bound of the two-sided 95% CI for difference of seroconversion rates (SCR) (SCR18-<26yo - SCR12-<18yo) was < 10%

Results

Participant flow



Recruitment

The paediatric expansion of Study 2019nCoV-301 was initiated on 26 April 2021 (first sentinel participant screened), and after safety review of sentinel participants on 06 May 2021, enrolment was resumed and completed on 05 June 2021 at 73 sites across the US.

The data cut-off date for this analysis was 27 September 2021, with data extraction on 06 October 2021.

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. The study remains ongoing through approximately 2 years of follow-up from the Day 21 injection.

Conduct of the study

Table 4. Summary of Major and Minor Protocol Deviations (All Randomised Participants)

Protocol Deviations	NVX-CoV2373 N = 1484	Placebo N = 748	Total N = 2232
Participants with at least 1 deviation N (%)	741 (49.9%)	395 (52.8%)	1136 (50.9%)
Major deviations N (%) participants	207 (13.9)	142 (19.0)	349 (15.6)
Study vaccine	130 (8.8)	97 (13.0)	227 (10.2)
Procedures/tests	21 (1.4)	12 (1.6)	33 (1.5)
ICF Issues	52 (3.5)	28 (3.7)	80 (3.6)
Laboratory	4 (0.3)	4 (0.5)	8 (0.4)
Inclusion/exclusion	3 (0.2)	0	3 (0.1)
Concomitant medications	12 (0.8)	8 (1.1)	20 (0.9)
Other	1 (< 0.1)	2 (0.3)	3 (0.1)
Minor deviations	629 (42.4)	318 (42.8)	947 (42.4)
Visit schedule	590 (39.8)	301 (40.2)	891 (39.9)
ICF Issues	33 (2.2)	16 (2.1)	49 (2.2)
Procedures/tests	23 (1.5)	20 (2.7)	43 (1.9)
Laboratory	12 (0.8)	0	12 (0.5)
Other	0	1 (0.1)	1 (< 0.1)

Abbreviations: ICF = informed consent form; NVX-CoV2373 = 5 µg SARS-CoV-2 rS with 50 µg Matrix-M1 adjuvant; SARSCoV-2 rS = severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine. Source: T14.1.3.1

In total, 1136 participants recorded at least 1 protocol deviation – 741 (49.9%) in the NVX-CoV2373 group compared with 395 (52.8%) in the placebo group. The majority (83.4%) of these deviations concerned minor protocol deviations, mostly relating to visit schedules.

Protocol deviations that were considered exclusionary for the PP-EFF and PP-IMM Analysis Sets occurred slightly more frequently in the placebo group than in the NVX-CoV2373 group.

Approximately 6.3% of participants were unblinded to study treatment assignment during the course of the study. The most frequent (incidence > 4.0%) reason for study unblinding was due to a participant request for EUA-approved vaccine (4.5%). There was a small imbalance between treatment groups in participants that requested unblinding with the intention to receive EUA vaccine, with a higher proportion of placebo recipients (5.3%) requesting unblinding than vaccine recipients (4.0%). It is speculated that this difference may reflect the perception of study participants based on their reactogenicity symptoms or serologic testing outside of the study.

Table 5. Summary of Protocol Deviations Leading to Censoring from PP-EFF and PP-IMM Analysis Sets (All Randomised Participants) (2019nCoV-301, Paediatric Expansion)

Protocol Deviations	NVX-CoV2373 N = 1484	Placebo N = 748	Total N = 2232
PP-EFF Analysis Set, n (%)			
Concomitant medications	12 (0.8)	8 (1.1)	20 (0.9)
Took prohibited medication during treatment	12 (0.8)	8 (1.1)	20 (0.9)
Study vaccine	3 (0.2)	8 (1.1)	11 (0.5)
Dosing non-compliance	2 (0.1)	2 (0.3)	4 (0.2)
Incorrect medication/randomization	1 (< 0.1)	5 (0.7)	6 (0.3)
Study vaccine administration error	0	1 (0.1)	1 (< 0.1)
Inclusion/exclusion	2 (0.1)	0	2 (< 0.1)
Did not meet inclusion/exclusion criteria	2 (0.1)	0	2 (< 0.1)
Visit schedule	1 (< 0.1)	3 (0.4)	4 (0.2)
Visit not done	0	1 (0.1)	1 (< 0.1)
Visit outside of protocol window	1 (< 0.1)	2 (0.3)	3 (0.1)
PP-IMM Analysis Set, n (%)			
Visit schedule	70 (4.7)	44 (5.9)	114 (5.1)
Visit outside protocol window	61 (4.1)	39 (5.2)	100 (4.5)
Visit not done	9 (0.6)	5 (0.7)	14 (0.6)
Concomitant medications	12 (0.8)	8 (1.1)	20 (0.9)
Took prohibited medication during treatment	12 (0.8)	8 (1.1)	20 (0.9)
Laboratory	8 (0.5)	2 (0.3)	10 (0.4)
Labs not done	8 (0.5)	2 (0.3)	10 (0.4)
Study vaccine	3 (0.2)	8 (1.1)	11 (0.5)
Dosing non-compliance	2 (0.1)	2 (0.3)	4 (0.2)
Incorrect medication/randomization	1 (< 0.1)	5 (0.7)	6 (0.3)
Participant took incorrect dose	0	1 (0.1)	1 (< 0.1)
Inclusion/exclusion	2 (0.1)	0	2 (< 0.1)
Did not meet inclusion/exclusion criteria	2 (0.1)	0	2 (< 0.1)

Abbreviations: NVX-CoV2373 = 5 µg SARS-CoV-2 rS with 50 µg Matrix-M1 adjuvant; PP-EFF = Per-Protocol Efficacy; PP-IMM = Per-Protocol Immunogenicity; SARS-CoV-2 rS = severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine.

Baseline data

The median age (range) of participants was 14.0 years (12 – 17 years), with 67.1% of adolescent participants being 12 to < 15 years of age. As EUA vaccine was available and recommended for adolescents 16 to < 18 years of age during the period this trial was enrolling, the goal of similar representation in the 12 to < 15 years and 15 to < 18 years subgroups was not achieved. Nearly half the adolescent participants were female, and most adolescent participants were White (74.4%) and not of Hispanic or Latino origin (81.3%). Approximately 27% of adolescent participants were obese (≥ 30.0 kg/m2), and approximately 16% of adolescent participants had either anti-NP serology or PCR-positivity evidence of prior exposure to SARSCoV-2 (Table 6).

Table 6. Demographics and Baseline Characteristics in Paediatric Expansion (Safety Analysis Set, 2019nCoV-301, paediatric expansion)

Parameter	NVX-CoV2373 N = 1487	Placebo N = 745	Total N = 2232
Age (years)			
Mean (SD)	13.9 (1.4)	13.8(1.4)	13.8 (1.4)
Median	14.0	14.0	14.0
Min, max	12, 17	12, 17	12, 17
Age group, n (%)			
12 to < 15 years	998 (67.1)	500 (67.1)	1498 (67.1)
15 to < 18 years	489 (32.9)	245 (32.9)	734 (32.9)
Sex, n (%)			
Male	756 (50.8)	416 (55.8)	1172 (52.5)
Female	731 (49.2)	329 (44.2)	1060 (47.5)
Race, n (%)			
White	1115 (75.0)	545 (73.2)	1660 (74.4)
Black or African American	202 (13.6)	108 (14.5)	310 (13.9)
American Indian or Alaska Native	32 (2.2)	14 (1.9)	46 (2.1)
Asian	43 (2.9)	34 (4.6)	77 (3.4)
Mixed origin	82 (5.5)	37 (5.0)	119 (5.3)
Native Hawaiian or Other Pacific Islander	3 (0.2)	2 (0.3)	5 (0.2)
Not reported	10 (0.7)	5 (0.7)	15 (0.7)
Ethnicity, n (%)			
Not Hispanic or Latino	1208 (81.2)	607 (81.5)	1815 (81.3)
Hispanic or Latino	274 (18.4)	138 (18.5)	412 (18.5)
Not reported	2 (0.1)	0	2 (< 0.1)
Unknown	3 (0.2)	0	3 (0.1)
Weight (kg)			
Mean (SD)	66.5 (21.82)	64.8 (21.23)	65.9 (21.63)
Median	61.7	59.9	61.0
Min, max	[redacted]		
BMI (kg/m²)			
Mean (SD)	24.3 (6.92)	23.7 (6.76)	24.1 (6.87)
Median	22.6	21.9	22.3
Min, max	[redacted]		
BMI category, n (%)			
Underweight (< 18.0 kg/m²)	40 (2.7)	28 (3.8)	68 (3.0)
Normal (18.0 – 24.9 kg/m²)	771 (51.8)	417 (56.0)	1188 (53.2)
Overweight (25.0 – 29.9 kg/m²)	270 (18.2)	107 (14.4)	377 (16.9)
Obese (≥ 30.0 kg/m²)	406 (27.3)	193 (25.9)	599 (26.8)
Height (cm)			
Mean (SD)	164.9 (10.34)	164.7 (10.36)	164.8 (10.35)
Median	165.0	164.3	165.0
Min, max	[redacted]		
SARS-CoV-2 serostatus, n (%)			
Anti-NP			
Positive	227 (15.3)	121 (16.2)	348 (15.6)
Negative	1254 (84.3)	623 (83.6)	1877 (84.1)
Missing	6 (0.4)	1 (0.1)	7 (0.3)
PCR			
Positive	12 (0.8)	9 (1.2)	21 (0.9)
Negative	1473 (99.1)	736 (98.8)	2209 (99.0)
Missing	2 (0.1)	0	2 (< 0.1)
Anti-NP/ PCR[1]			
Positive	234 (15.7)	125 (16.8)	359 (16.1)
Negative	1252 (84.2)	620 (83.2)	1872 (83.9)
Missing	1 (< 0.1)	0	1 (< 0.1)

Abbreviations: BMI = body mass index; max = maximum; min = minimum; NVX-CoV2373 = 5 µg SARS-CoV-2 rS with 50 µg Matrix-M1 adjuvant; PCR = polymerase chain reaction; NP = nucleoprotein; SARS-CoV-2 rS = severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine; SD = standard deviation. 1. Participants with either anti-NP or PCR were reported. Source: T14.1.6.1

Considering relevant comorbidities, n=171 (7.7%) reported Asthma in their medical history (115 and 56 in the NVX-CoV2373 and placebo group respectively) and few participants (<0.1) had either type 1 or

type 2 diabetes mellitus in their medical history. Cardiac disorders, including POTS, were recorded in the medical history of 0.4% of participants.

Demographics and baseline characteristics of the PP-EFF Analysis Set were also well balanced between the 2 treatment groups and similar to those of the Safety Analysis Set, except that no participants were seropositive or PCR-positive. Demographics and baseline characteristics of the PP-IMM Analysis Set were also well balanced between the 2 treatment groups.

The demographics and baseline characteristics of the random subset of adolescents and adults for the primary immunogenicity objective are presented below.

Table 7. Demographics and Baseline Characteristics of Participants Vaccinated with NVX-CoV2373 Randomly Selected for Neutralising Antibody Non-inferiority Comparison (Primary Immunogenicity Objective)

Parameter	Adults 18 − < 26 years (N=416)	Adolescents 12 − < 18 years (N=390)
Age (years)		
Mean (SD)	21.9 (2.28)	13.7 (1.30)
Median	22.0	14.0
Min, max	18 − 25	12 − 17
Age group, n (%)		
12 to < 15 years	n/a	274 (70.3)
15 to < 18 years	n/a	116 (29.7)
Sex, n (%)		
Male	194 (46.6)	204 (52.3)
Female	222 (53.4)	186 (47.7)
Race, n (%)		
White	290 (69.7)	309 (79.2)
Black or African American	43 (10.3)	45 (11.5)
American Indian or Alaska Native	36 (8.7)	5 (1.3)
Asian	31 (7.5)	10 (2.6)
Mixed origin	7 (1.7)	20 (5.1)
Native Hawaiian or Other Pacific Islander	2 (0.5)	0
Not reported	7 (1.7)	1 (0.3)

Ethnicity, n (%)		
Not Hispanic or Latino	281 (67.5)	325 (83.3)
Hispanic or Latino	134 (32.2)	65 (16.7)
Not reported	1 (0.2)	0
Unknown	0	0
Height (cm)		
Mean (SD)	170.8 (10.40)	165.1 (9.61)
Median	170.2	165.1
Min - Max	[redacted]	
Weight (kg)		
Mean (SD)	78.1 (22.15)	65.0 (20.22)
Median	74.4	60.6
Min - Max	[redacted]	
BMI (kg/m^2)		
Mean (SD)	26.6 (6.83)	23.6 (6.31)
Median	25.2	22.1
Min - Max	[redacted]	
SARS-CoV-2 serostatus, n (%)		
Anti-NP/ PCR		
Positive	0	0
Negative	416 (100)	390 (100)
Missing	0	0

Numbers analysed

Of the 2,247 adolescent participants randomised, 2,247 (100%) were in the ITT Analysis Set, 2,232 (99.3%) were in the FAS and Safety Analysis Sets, 1,799 (80.1%) were in the PP-EFF Analysis Set, and 1,974 (87.9%) were in the PP-IMM (Day 35) Analysis Set.

Table 8. Analysis Sets (All Randomised Participants, 2019nCoV-301, Paediatric Expansion)

Analysis Sets	NVX-CoV2373	Placebo	Total
ITT	1491 (100)	756 (100)	2247 (100)
FAS	1484 (99.5)	748 (98.9)	2232 (99.3)
Safety	1487	745	2232
PP-EFF	1205 (80.8)	594 (78.6)	1799 (80.1)
PP-EFF-2	1423 (95.4)	704 (93.1)	2127 (94.7)
PP-IMM (Day 35)	1120 (75.1)	534 (70.6)	1654 (73.6)
PP-IMM-2 (Day 35)	1330 (89.2)	644 (85.2)	1974 (87.9)

Table 9. Reasons for Exclusion from the Analysis Sets (All Randomised Participants, 2019nCoV-301, Paediatric Expansion)

Analysis Sets	NVX-CoV2373 N = 1491	Placebo N = 756	Total N = 2247
ITT	1491 (100)	756 (100)	2247 (100)
Excluded	0	0	0
FAS	1484 (99.5)	748 (98.9)	2232 (99.3)
Excluded (never dosed)	7 (0.5)	8 (1.1)	15 (0.7)
Safety	1487	745	2232
Excluded (never dosed)	7 (0.5)	8 (1.1)	15 (0.7)
PP-EFF	1205 (80.8)	594 (78.6)	1799 (80.1)
Excluded	286 (19.2)	162 (21.4)	448 (19.9)
Baseline positive anti-NP result	227 (15.2)	121 (16.0)	348 (15.5)
Censored prior to Dose 2 + 7 days	30 (2.0)	20 (2.6)	50 (2.2)
Did not complete vaccination schedule	26 (1.7)	23 (3.0)	49 (2.2)
Randomized but never dosed	7 (0.5)	8 (1.1)	15 (0.7)
Baseline positive PCR result	12 (0.8)	9 (1.2)	21 (0.9)
PP-EFF-2	1423 (95.4)	704 (93.1)	2127 (94.7)
Excluded	68 (4.6)	52 (6.9)	120 (5.3)
Censored prior to Dose 2 + 7 days	30 (2.0)	20 (2.6)	50 (2.2)
Did not complete vaccination schedule	26 (1.7)	23 (3.0)	49 (2.2)
Randomized but never dosed	7 (0.5)	8 (1.1)	15 (0.7)
Baseline positive PCR result	12 (0.8)	9 (1.2)	21 (0.9)
PP-IMM (Day 35)	1120 (75.1)	534 (70.6)	1654 (73.6)
Excluded	371 (25.0)	222 (29.4)	593 (26.4)
SARS-CoV-2 exposure at baseline	210 (14.1)	110 (14.6)	320 (14.2)
Did not complete vaccination schedule	26 (1.7)	23 (3.0)	49 (2.2)
Randomized but never dosed	7 (0.5)	8 (1.1)	15 (0.7)
Sample not collected	85 (5.7)	63 (8.3)	148 (6.6)
Infection prior to visit	7 (0.5)	6 (0.8)	13 (0.6)
Protocol deviation	69 (4.6)	43 (5.7)	112 (5.0)
PP-IMM-2 (Day 35)	1330 (89.2)	644 (85.2)	1974 (87.9)
Excluded	161 (10.8)	112 (14.8)	273 (12.1)
Did not complete vaccination schedule	26 (1.7)	23 (3.0)	49 (2.2)
Randomized but never dosed	7 (0.5)	8 (1.1)	15 (0.7)
Sample not collected	85 (5.7)	63 (8.3)	148 (6.6)
Infection prior to visit	7 (0.5)	6 (0.8)	13 (0.6)
Protocol deviation	69 (4.6)	43 (5.7)	112 (5.0)

Abbreviations: FAS = Full Analysis Set; ITT = Intent-to-Treat; NP = nucleoprotein; NVX-CoV2373 = 5 µg SARS-CoV-2 rS with 50 µg Matrix-M1 adjuvant; PCR = polymerase chain reaction; PP-EFF = Per-Protocol Efficacy; PP-EFF-2 = Per- Protocol Efficacy 2; PP-IMM = Per-Protocol Immunogenicity; PP-IMM-2 = Per-Protocol Immunogenicity 2; SARS-CoV-2 rS = severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine. Source: T14.1.2

Outcomes and estimation

Primary immunogenicity endpoint

NI of the neutralising antibody response at Day 35 for adolescent participants seronegative to anti-SARS-CoV-2 NP antibodies/PCR-negative at baseline compared with that observed in seronegative/PCR-negative adult participants 18 to < 26 years of age from the adult part of the study (Immunogenicity Population participants before crossover) was met:

- The upper bound of two-sided 95% CI for the ratio of GMTs (GMT18-<26yo/GMT12-<18yo) was < 1.5: GMR 0.7, 95% CI: 0.6, **0.8**
- The point estimate of the ratio of GMTs was ≤ 1.22 (estimated as square root of 1.5): GMR **0.7**, 95% CI: 0.6, 0.8
- The upper bound of the two-sided 95% CI for difference of seroconversion rates (SCR18-<26yo – SCR12-<18yo) was < 10%: SCR difference 1.1, 95% CI: -0.2, **2.8.**

Table 10. Adjusted Ratio of Geometric Mean and Difference in Seroconversion Rate of MN Assay Neutralising Antibody Titers for SARS-CoV-2 S Wild-Type Virus at Day 35 Overall and Stratified by Age Group (PP-IMM Analysis Set, 2019nCoV-301, paediatric expansion)

Parameters	Adult Main Study (18 to < 26 Years) N = 416	Pediatric Expansion (12 to < 18 Years) N = 390	Parameter	Adult Main Study (18 to < 26 Years) Vs Pediatric Expansion (12 to < 18 Years)
MN (1/dilution)				
Day 0				
n	416	390	---	---
GMT	10.3	10.4	---	---
95% CI[1]	(10.0, 10.5)	(10.0,10.7)	---	---
Day 35				
n	416	390	n1*, n2*	416, 390
GMT	2633.6	3859.6	GMR[2]	0.7
95% CI[2]	(2388.6, 2903.6)	(3422.8, 4352.1)	95% CI	(0.6, 0.8)
Day 35 seroconversion				
n3	415	385		
SCR[3]	99.8	98.7	Difference	1.1
95% CI[3]	(98.7, 100.0)	(97.0, 99.6)	95% CI[4]	(-0.2, 2.8)

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; n = number of participants with non-missing response at each visit; n1* = number of participants in adult part of study (18 to < 26 years) with non-missing neutralising antibodies result at both Day 0 and Day 35; n3 = number of participants who reported a ≥ 4-fold increase; PP-IMM = Per-Protocol Immunogenicity; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SCR = seroconversion rate.
1. The 95% CI for GMT was calculated based on the t-distribution of the log-transformed values, then back transformed to the original scale for presentation.
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. SCR is defined as percentage of participants with a ≥ 4-fold difference in titers between Day 35 and Day 0. The 95% CI for SCR was calculated using the Clopper-Pearson exact method.
4. Difference in SCR in the adult part of the study for 18 to < 26 year olds minus SCR in the paediatric expansion. The 95% CI for the difference of SCR between groups was calculated with the method of Miettinen and Nurminen. Note: table includes participants in the active vaccine group only.

Source: T14.2.7.2.1

Post hoc immunogenicity tables (i.e., non-inferiority of the neutralising antibody response and the summary of the neutralising antibodies for SARS-CoV-2 Wild-Type Virus at Day 0 and Day 35 in by age group) expressed in international units (IU)/mL are presented below.

Table 11. Geometric Mean Titers and Seroconversion Rate of MN Assay Neutralising Antibody Titers for SARS-CoV-2 S Wild-Type Virus at Day 35 Overall and Stratified by Age Group (PP-IMM Analysis Set), converted to International Units (IU)

Parameters	Adult Main Study (18 to < 26 Years) N = 416	Pediatric Expansion (12 to < 18 Years) N = 390
MN (1/dilution)		
Day 0		
n	416	390
GMT	6.4	6.4
95% CI[1]	6.2, 6.5	6.2, 6.6
Day 35		
n	416	390
GMT	1632.8	2393.0
95% CI[1]	1480.9, 1800.2	2122.2, 2698.3
Day 35 seroconversion		
n3	415	385
SCR[2]	99.8	98.7
95% CI[1]	98.7, 100.0	97.0, 99.6

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; GMT = geometric mean titer; LLOQ = lower limit of quantitation; MN = microneutralization; N = number of participants in assay-specific PP-IMM Analysis Set in each part of study; n = number of participants with non-missing response at each visit; n3 = number of participants who reported a ≥ 4-fold increase; PP-IMM = Per-Protocol Immunogenicity; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SCR = seroconversion rate.

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

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

Note: table includes participants in the active vaccine group only.

Primary efficacy endpoint

Vaccine Efficacy against PCR-Confirmed Symptomatic Mild, Moderate, or Severe COVID-19 with Onset from at Least 7 Days after Second Vaccination in Baseline Serologically Negative/PCR-negative Adolescent Participants

There was a total of 20 cases of PCR-confirmed symptomatic mild, moderate, or severe COVID-19 with onset from at least 7 says after second vaccination in the PP-EFF Analysis Set; 6 (0.5%) in the NVX-CoV2373 group and 14 (2.4%) in the placebo group, all of which were mild in severity. Case distribution resulted in a VE of NVX-CoV2373 for preventing symptomatic mild, moderate, or severe COVID-19 in baseline seronegative/ PCR—negative adolescent participants of 79.54% (95% CI: 46.83, 92.13). Sensitivity analysis resulted in a VE of 79.39% (95% CI: 46.34, 92.08).

Table 12. Vaccine Efficacy against PCR-Confirmed Symptomatic Mild, Moderate, or Severe COVID-19 with Onset from at Least 7 Days after Second Vaccination in Baseline Serologically Negative/PCR-negative Adolescent Participants (PP-EFF Analysis Set)

Parameter	NVX-CoV2373 N = 1205	Placebo N = 594
Participants with no occurrence of event[1], n (%)	1199 (99.5)	580 (97.6)
Participants with occurrence of event[2], n (%)	6 (0.5)	14 (2.4)
Severity of first occurrence, n (%)		
Mild	6 (0.5)	14 (2.4)
Moderate	0	0
Severe	0	0
Median surveillance time[3] (days)	64.0	63.0
Log-linear model using modified Poisson regression[4]		
Mean disease incidence rate per year in 100 people	2.90	14.20
95% CI	1.31, 6.46	8.42, 23.93
Relative risk	0.20	
95% CI	0.08, 0.53	
Vaccine efficacy (%)	79.54	
95% CI	46.83, 92.13	
Cox proportional hazard model (sensitivity analysis)[5]		
Vaccine efficacy (%)	79.39	
95% CI	46.34, 92.08	

Abbreviations: CI = confidence interval; COVID-19 = coronavirus disease 2019; NVX-CoV2373 = 5 µg SARS-CoV-2 rS with 50 µg Matrix-M1 adjuvant; PCR = polymerase chain reaction; PP-EFF = Per-Protocol Efficacy; SARS-CoV-2 rS = severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine; VE = vaccine efficacy.
1. Includes participants with PCR-confirmed infection who did not meet mild, moderate, or severe COVID-19 criteria.
2. Event = first occurrence of PCR-confirmed mild, moderate, or severe COVID-19 with onset of illness episode from at least 7 days after second vaccination within the surveillance period.
3. Surveillance time was defined as the difference between the date at end of surveillance period (onset of first occurrence of event, or follow up contact at 12 months after last vaccination, or censoring) and date at start of surveillance period (from at least 7 days after second vaccination) + 1.
4. Modified Poisson regression with logarithmic link function, treatment group, and strata as fixed effects and robust error variance [Zou 2004].
5. Cox-proportional hazard model with Efron's method for tie handling with vaccine group and age strata. Hazard ratio was used to estimate relative risk. Source: T14.2.1.1.1, T14.2.1.1.2, T14.2.1.1.3.1

Secondary immunogenicity endpoints

Neutralising Ab response by age group: Across the 2 age subgroups (12 to < 15 years of age and 15 to < 18 years of age), non-inferiority analyses of the MN responses were in line compared to the overall results:

- 12 to < 15 Years
    - The GMT at D35 in children aged 12 to <15 was 4161 (95%CI: 3642, 4753). The GMT at D35 in adults 18 to <26 years from the adult main study was 2634 (95%CI: 2389, 2904).
    - The upper bound of two-sided 95% CI for the ratio of GMTs ($GMT_{18-<26yo}/GMT_{12-<15yo}$) was < 1.5: GMR 0.6, 95% CI: 0.5, 0.7.
    - The point estimate of the ratio of GMTs was ≤ 1.22 (estimated as square root of 1.5): GMR 0.6, 95% CI: 0.5, 0.8
    - The SCR at D35 in children aged 12 to <15 was 99.3% (95% CI: 97.4, 99.9)
    - The upper bound of the two-sided 95% CI for difference of seroconversion rates ($SCR_{18-<26yo} - SCR_{12-<15yo}$) was < 10%: SCR difference 0.5, 95% CI: -0.7, 2.4.

- 15 to < 18 Years
    - The GMT at D35 in children aged 15 to <18 was 3232 (95%CI: 3642, 4753). The GMT at D35 in adults 18 to <26 years from the adult main study was 2634 (95%CI: 2389, 2904).
    - The upper bound of two-sided 95% CI for the ratio of GMTs ($GMT_{18-<26yo}/GMT_{15-<18yo}$) was < 1.5: GMR 0.8, 95% CI: 0.7, 1.0
    - The point estimate of the ratio of GMTs was ≤ 1.22 (estimated as square root of 1.5): GMR 0.8, 95% CI: 0.7, 1.0
    - The SCR at D35 in children aged 15 to <18 was 97.4% (95% CI:92.6, 99.5)
    - The upper bound of the two-sided 95% CI for difference of seroconversion rates ($SCR_{18<26yo} - SCR_{15-<18yo}$) was < 10%: SCR difference 2.4, 95% CI: 0.5, 7.1

Table 13. Summary of MN Assay Neutralising Antibodies for SARS-CoV-2 Wild-Type Virus at Day 0 (Baseline) and Day 35 (14 Days after Second Vaccination) in Baseline Serologically Negative/PCR-negative Adolescent Participants by Age Group (PP-IMM Analysis Set)

Parameters	Participants 12 to < 18 Years		Participants 12 to < 15 Years		Participants 15 to < 18 Years	
	NVX-CoV2373 N = 390	Placebo N = 35	NVX-CoV2373 N = 274	Placebo N = 24	NVX-CoV2373 N = 116	Placebo N = 11
Day 0 (baseline)[1]						
n1	390	35	274	24	116	11
Median (1/dilution)	10.0	10.0	10.0	10.0	10.0	10.0
Min, max (1/dilution)	10, 1280	10, 10	10, 160	10, 10	10, 1280	10, 10
GMT	10.4	10.0	10.2	10.0	10.7	10.0
95% CI[2]	10.0, 10.7	10.0, 10.0	10.0, 10.5	10.0, 10.0	9.8, 11.7	10.0, 10.0
Day 35						
n1	390	35	274	24	116	11
Median (1/dilution)	5120.0	10.0	5120.0	10.0	5120.0	10.0
Min, max (1/dilution)	10, 81920	10, 10240	10, 81920	10, 10240	10, 40960	10, 10
GMT	3859.6	12.2	4160.8	13.3	3231.8	10.0
95% CI[2]	3422.8, 4352.1	8.2, 18.2	3642.4, 4753.1	7.3, 24.3	2507.4, 4165.6	10.0, 10.0
n2	390	35	274	24	116	11
GMFR referencing Day 0	372.5	1.2	406.7	1.3	302.6	1.0
95% CI[2]	329.1, 421.5	0.8, 1.8	355.1, 465.9	0.7, 2.4	232.3, 394.3	1.0, 1.0
SCR ≥ 4-fold increase, n3/n2 (%)[3]	385/390 (98.7)	1/35 (2.9)	272/274 (99.3)	1/24 (4.2)	113/116 (97.4)	0/11 (0)
95% CI[4]	97.0, 99.6	0.1, 14.9	97.4, 99.9	0.1, 21.1	92.6, 99.5	0.0, 28.5

Abbreviations: CI = confidence interval; GMFR = geometric mean fold rise; GMT = geometric mean titer; LLOQ = lower limit of quantification; max = maximum; Min = minimum; MN = microneutralisation; n1 = number of participants in the PP-IMM Analysis Set with non-missing data at visit; n2 = number of participants in the PP-IMM Analysis Set with non-missing data at both the baseline and Day 35 visit; n3 = number of participants who reported ≥ 4-fold increase. Percentages were calculated based on n2 as the denominator; NVX-CoV2373 = 5 µg SARS-CoV-2 rS + 50 µg Matrix-M adjuvant; PP-IMM = Per-Protocol Immunogenicity; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SARS-CoV-2rS = NVX-CoV2373; SCR = seroconversion rate.

1. Day 0 (baseline) was defined as the last non-missing assessment prior to study vaccine administration.
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. The SCR percentage was defined as percentage of participants at each post vaccination visit with a ≥ 4-fold rise in antibody concentration.
4. The 95% CI for SCR percentage was calculated using the exact Clopper-Pearson method.

Note, titer values less than LLOQ (20) were replaced by 0.5 × LLOQ.

Neutralising Antibody Levels by Baseline Serostatus (PP-IMM-2 Analysis Set): Neutralising antibodies specific for SARS-CoV-2 wild-type virus at Day 35 (14 days after second vaccination) in both baseline serologically negative/PCR-negative and baseline serologically or PCR-positive adolescent participants were increased relative to placebo and showed similar patterns of response, with higher levels in the placebo group in serologically or PCR-positive adolescent participants; this latter response was clearly evident in serologically or PCR-positive adolescent participants. Participants were labelled as serologically negative for the immunogenicity populations if their baseline anti-NP and PCR results were negative or missing. Participants were labelled serologically positive for these populations if their baseline anti-NP or

PCR results were positive. At 2 weeks following second vaccination in most participants (Day 35), neutralising antibody GMTs in the NVX-CoV2373 group were markedly increased relative to placebo for all participants (4,429.3 vs 21.3, respectively); for baseline serologically or PCR-positive participants (9,151.3 vs 149.3) relative to placebo; and for baseline serologically negative/PCR negative participants (3,859.6 vs 12.2), with no evidence of placebo response (Table 14). Neutralising antibody GMTs in the NVX-CoV2373 group were approximately 2.4-fold higher in the baseline serologically or PCR-positive cohort than in the baseline serologically negative/PCR-negative cohort.

Table 14. Summary of MN Assay Neutralising Antibodies for SARS-CoV-2 Wild-Type Virus at Day 0 (Baseline) and Day 35 (14 Days after Second Vaccination) in Adolescent Participants by Baseline Serostatus (PP-IMM-2 Analysis Set)

Parameters	Serologically Negative or Positive		Serologically Negative		Serologically Positive	
	NVX-CoV2373 N = 464	Placebo N = 45	NVX-CoV2373 N = 390	Placebo N = 35	NVX-CoV2373 N = 74	Placebo N = 10
Day 0 (baseline)[1]						
n1	464	45	390	35	74	10
Median (1/dilution)	10.0	10.0	10.0	10.0	160.0	120.0
Min, max (1/dilution)	10, 2560	10, 2560	10, 1280	10, 10	10, 2560	40, 2560
GMT	15.6	19.1	10.4	10.0	135.2	183.8
95% CI[2]	14.1, 17.3	12.6, 28.9	10.0, 10.7	10.0, 10.0	101.8, 179.5	66.7, 506.4
Day 35						
n1	464	45	390	35	74	10
Median (1/dilution)	5120.0	10.0	5120.0	10.0	10240.0	120.0
Min, max (1/dilution)	10, 81920	10, 10240	10, 81920	10, 10240	320, 81920	20, 1280
GMT	4429.3	21.3	3859.6	12.2	9151.3	149.3
95% CI[2]	3964.9, 4948.2	13.2, 34.2	3422.8, 4352.1	8.2, 18.2	7291.8, 11485.1	59.6, 374.1
n2	464	45	390	35	74	10
GMFR referencing Day 0	283.8	1.1	372.5	1.2	67.7	0.8
95% CI[2]	249.4, 322.9	0.8, 1.6	329.1, 421.5	0.8, 1.8	48.8, 93.9	0.5, 1.4
SCR ≥ 4-fold increase, n3/n2 (%)[3]	458/464 (98.7)	1/45 (2.2)	385/390 (98.7)	1/35 (2.9)	73/74 (98.6)	0/10 (0)
95% CI[4]	97.2, 99.5	0.1, 11.8	97.0, 99.6	0.1, 14.9	92.7, 100.0	0.0, 30.8

Abbreviations: CI = confidence interval; GMFR = geometric mean fold rise; GMT = geometric mean titer; LLOQ = lower limit of quantification; max = maximum; Min = minimum; MN = microneutralisation; n1 = number of participants in the PP-IMM-2 Analysis Set with non-missing data at visit; n2 = number of participants in the PP-IMM-2 Analysis Set with non-missing data at both the baseline and Day 35 visit; n3 = number of participants who reported ≥ 4-fold increase. Percentages were calculated based on n2 as the denominator; NVX-CoV2373 = 5 µg SARS-CoV-2 rS + 50 µg Matrix-M adjuvant; PP-IMM-2 = Per-Protocol Immunogenicity 2; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SARS-CoV-2rS = NVX-CoV2373; SCR = seroconversion rate.

1. Day 0 (baseline) was defined as the last non-missing assessment prior to study vaccine administration.
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. The SCR percentage was defined as percentage of participants at each post vaccination visit with a ≥ 4-fold rise in antibody concentration.
4. The 95% CI for SCR percentage was calculated using the exact Clopper-Pearson method.

Note, titer values less than LLOQ (20) were replaced by 0.5 × LLOQ

Serum IgG response by baseline serostatus: Serum IgG levels specific to SARS-CoV-2 rS protein were measured in all adolescent participants at Day 0 (baseline) and Day 35 (14 days after second vaccination) using a validated anti-S IgG ELISA (Novavax Clinical Immunology, Gaithersburg, MD, US). The LLOQ for this assay was 200 ELISA units per mL (EU/mL), with titers below this level documented as 100 EU/mL.

At Day 0 (baseline), serum IgG antibody GMEUs were 194.9 and 211.6 in all NVX-CoV2373 and placebo recipients respectively regardless of baseline serostatus; 3,737.3 and 4,403.2 in serologically or PCR-positive NVX-CoV2373 and placebo recipients; and 112.3 and 113.2 in baseline serologically negative/PCR-negative NVX-CoV2373 and placebo recipients.

At 2 weeks following second vaccination in most participants (Day 35), serum IgG antibody GMEUs in the NVX-CoV2373 group were markedly increased relative to placebo for all participants (147,078.4 vs 255.8, respectively); for baseline serologically or PCR-positive participants (210,423.5 vs 4,214.2) relative to placebo; and for baseline serologically negative/PCR-negative participants (137,671.2 vs 143.6), with no evidence of placebo response. Serum IgG antibody GMEUs in the NVX-CoV2373 group were approximately 1.5-fold higher in the baseline serologically positive or PCR-positive cohort than in the baseline serologically negative/PCR-negative cohort.

Neutralising Antibody Levels by Sex

Table 15. Summary of MN assay neutralising antibodies for SARS-CoV-2 wild-type virus at Day 0 (baseline) and Day 35 (14 days after second vaccination) in baseline serologically negative/PCR-negative adolescents participants by Sex (PP-IMM analysis set)

Parameters	Female		Male	
	NVX-CoV2373 N = 186	Placebo N = 15	NVX-CoV2373 N = 204	Placebo N = 20
Day 0 (baseline)[1]				
n1	186	15	204	20
Median (1/dilution)	10.0	10.0	10.0	10.0
Min, max (1/dilution)	10, 80	10, 10	10, 1280	10, 10
GMT	10.3	10.0	10.5	10.0
95% CI[2]	9.9, 10.6	10.0, 10.0	9.9, 11.0	10.0, 10.0
Day 35				
n1	186	15	204	20
Median (1/dilution)	5120.0	10.0	5120.0	10.0
Min, max (1/dilution)	10, 20480	10, 10	10, 81920	10, 10240
GMT	3347.9	10.0	4394.1	14.1
95% CI[2]	2832.5, 3957.0	10.0, 10.0	3703.0, 5214.0	6.8, 29.2
n2	186	15	204	20
GMFR referencing Day 0	326.2	1.0	420.4	1.4
95% CI[2]	275.3, 386.4	1.0, 1.0	351.6, 502,8	0.7, 2.9
SCR ≥ 4-fold increase, n3/n2 (%)[3]	184/186 (98.9)	0/15 (0.0)	201/204 (98.5)	1/20 (5.0)
95% CI[4]	96.2, 99.9	0.0, 21.8	95.8, 99.7	0.1, 24.9

Abbreviations: CI = confidence interval; GMFR = geometric mean fold rise; GMT = geometric mean titer; LLOQ = lower limit of quantification; max = maximum; Min = minimum; MN = microneutralization; n1 = number of participants in the PP-IMM Analysis Set with non-missing data at visit; n2 = number of participants in the PP-IMM Analysis Set with non-missing data at both the baseline and Day 35 visit; n3 = number of participants who reported ≥ 4-fold increase. Percentages were calculated based on n2 as the denominator; NVX-CoV2373 = 5 µg SARS-CoV-2 rS + 50 µg Matrix-M adjuvant; PP-IMM = Per-Protocol Immunogenicity; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SARS-CoV-2rS = NVX-CoV2373; SCR = seroconversion rate.

[1] Day 0 (baseline) was defined as the last non-missing assessment prior to study vaccine administration.

[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] The SCR percentage was defined as percentage of participants at each post vaccination visit with a ≥ 4-fold rise in antibody concentration.

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

Note, titer values less than LLOQ (20) were replaced by 0.5 × LLOQ.

Serum IgG response by age: Responses are summarised in Table 16

At 2 weeks following second vaccination (Day 35), serum IgG antibody GMEUs in the NVXCoV2373 group were markedly increased relative to placebo across the age groups with no evidence of placebo response. Serum IgG antibody GMEUs in the NVX-CoV2373 group were approximately 1.2-fold higher in the younger age cohort (12 to < 15 years of age) than in the older age cohort (15 to < 18 years of age).

These immune responses equated to serum IgG antibody GMFRs relative to baseline (Day 0) of 1,226.1, 1,309.7, and 1,064.7, respectively, across the 3 age groups in the NVX-CoV2373 groups. SCRs in the NVX-CoV2373 groups also were increased relative to placebo across all age groups.

Table 16. Summary of Serum IgG Antibody Concentrations to SARS-CoV-2 S Protein at Day 0 (Baseline) and Day 35 (14 Days after Second Vaccination) in Baseline Serologically Negative/PCR-negative Adolescent Participants by Age Group (PP-IMM Analysis Set)

Parameters	Participants 12 to < 18 Years		Participants 12 to < 15 Years		Participants 15 to < 18 Years	
	NVX-CoV2373 N = 1118	Placebo N = 534	NVX-CoV2373 N = 762	Placebo N = 366	NVX-CoV2373 N = 356	Placebo N = 168
Day 0 (baseline)[1]						
n1	1118	534	762	366	356	168
Median (EU/mL)	100.0	100.0	100.0	100.0	100.0	100.0
Min, max (EU/mL)	100, 295412	100, 5880	100, 4657	100, 5880	100, 295412	100, 3620
GMEU	112.3	113.2	111.3	110.5	114.3	119.3
95% CI[2]	108.7, 116.0	108.8, 117.8	107.9, 114.9	105.9, 115.3	105.9, 123.4	109.5, 130.0
Day 35						
n1	1118	534	762	366	356	168
Median (EU/mL)	153837.0	100.0	155884.5	100.0	145854.0	100.0
Min, max (EU/mL)	100, 1211107	100, 361271	100, 1211107	100, 350053	100, 1009999	100, 361271
GMEU	137671.2	143.6	145817.4	134.4	121731.9	165.8
95% CI[2]	129578.0, 146269.8	128.6, 160.4	136708.7, 155532.9	120.0, 150.7	106835.9, 138704.7	129.3, 212.7
n2	1118	534	762	366	356	168
GMFR referencing Day 0	1226.1	1.3	1309.7	1.2	1064.7	1.4
95% CI[2]	1145.2, 1312.8	1.1, 1.4	1217.4, 1408.9	1.1, 1.4	919.8, 1232.5	1.1, 1.8
SCR ≥ 4-fold increase, n3/n2 (%)[3]	1104/1118 (98.7)	23/534 (4.3)	757/762 (99.3)	14/366 (3.8)	347/356 (97.5)	9/168 (5.4)
95% CI[4]	97.9, 99.3	2.7, 6.4	98.5, 99.8	2.1, 6.3	95.3, 98.8	2.5, 9.9

Abbreviations: CI = confidence interval; ELISA = enzyme-linked immunosorbent assay; EU/mL = ELISA units per milliliter; GMEU = geometric mean ELISA units; GMFR = geometric mean fold rise; IgG = immunoglobulin G; LLOQ = lower limit of quantification; max = maximum; Min = minimum; n1 = number of participants in the PP-IMM Analysis Set with non-missing data at visit; n2 = number of participants in the PP-IMM Analysis Set with non-missing data at both the baseline and Day 35 visit; n3 = number of participants who reported ≥ 4-fold increase. Percentages were calculated based on n2 as the denominator; NVX-CoV2373 = 5 µg SARS-CoV-2 rS + 50 µg Matrix-M adjuvant; PP-IMM = Per-Protocol Immunogenicity; S = spike; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SARS-CoV-2rS = NVXCoV2373; SCR = seroconversion rate.

1. Day 0 (baseline) was defined as the last non-missing assessment prior to study vaccine administration.
2. The 95% CI for GMEU and GMFR were calculated based on the t-distribution of the log-transformed values, then back transformed to the original scale for presentation.
3. The SCR percentage was defined as percentage of participants at each post vaccination visit with a ≥ 4-fold rise in antibody concentration.
4. The 95% CI for SCR percentage was calculated using the exact Clopper-Pearson method.

Note, concentration values less than LLOQ (200 EU/mL) were replaced by 0.5 × LLOQ.

Secondary efficacy endpoints

All cases were mild in severity. There were no moderate or severe cases of COVID-19 among NVX-CoV2373 or placebo adolescent recipients.

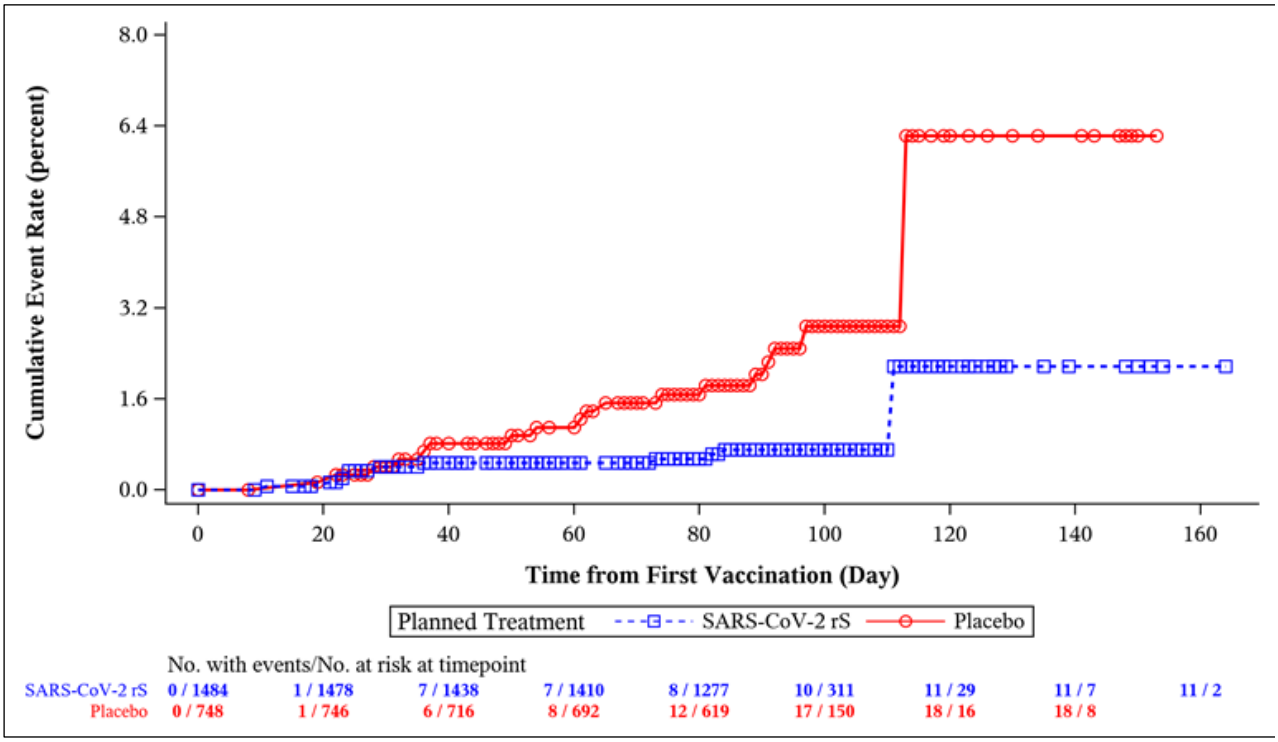
Of the 20 primary endpoint cases in the PP-EFF Analysis Set, viral genetic sequences were available for 11 samples (55%) from adolescent participants with PCR confirmed symptomatic mild, moderate, or severe COVID-19, 3 (0.2%) in the NVX-CoV2373 group and 8 (1.3%) in the placebo group with all cases classified as Delta VOC, resulting in an estimated VE of 82.0% (95% CI: 32.4, 95.2) due to a SARS-CoV-2 variant considered as a VOC/VOI, which was represented only by the Delta VOC.

The PP-EFF-2 analysis of the primary efficacy endpoint in adolescent participants regardless of baseline serostatus was similar to that of the PP-EFF analysis. There were 21 cases of PCR-confirmed symptomatic mild, moderate, or severe COVID-19 with onset from at least 7 days after second vaccination accrued for this analysis, with 6 (0.4%; all mild cases) in the NVX-CoV2373 group and 15 (2.1%; all mild cases) in the placebo group. NVX-CoV2373 prevented PCR-confirmed symptomatic mild, moderate, or severe COVID-19 with onset from at least 7 days after second vaccination in adolescent participants regardless of baseline serostatus with results similar to those of the primary efficacy endpoint (VE = 80.8% [95% CI: 50.5, 92.5]).

There were a total of 29 cases of PCR-confirmed symptomatic mild, moderate, or severe COVID-19 with onset from first vaccination (FAS); 11 (0.7%) in the NVX-CoV2373 group and 18 (2.4%) in the placebo group, all of which were mild in severity. NVX-CoV2373 prevented PCR-confirmed symptomatic mild, moderate, or severe COVID-19 with onset from first injection in adolescent participants regardless of baseline serostatus (VE = 69.74 [95% CI: 36.00, 85.69]).

Cumulative rates of PCR-confirmed symptomatic mild, moderate, and severe COVID-19 begin to diverge between 20 and 40 days after first vaccination.

Figure 1: Cumulative Incidence Curve of PCR-Confirmed Mild, Moderate, or Severe COVID-19 Disease with Onset from First Vaccination in Adolescent Participants Who Received at Least 1 Dose of Study Vaccine Regardless of Baseline Serostatus (FAS)



Abbreviations: COVID-19 = coronavirus disease 2019; FAS = Full Analysis Set; NVX-CoV2373 = 5 µg SARS-CoV-2 rS with 50 µg Matrix-M1 adjuvant; PCR = polymerase chain reaction; SARS-CoV-2 rS = severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine.

There were no cases in the per-protocol analysis set (PP-EFF) that did not meet the mild, moderate, or severe COVID-19 definition set forth in the protocol. Thus, VE against any symptomatic SARS-CoV-2 infection (PCR-positive nasal swab and ≥ 1 of any of the symptoms in the section "Clinical presentation, diagnosis") was identical to that against mild, moderate, or severe COVID-19: 79.5% (95% CI 46.8, 92.1).

Ancillary analyses

Efficacy by subgroup

Subgroup analyses based on key demographic and baseline characteristics were performed on the PP-EFF Analysis Set. VEs of NVX-CoV2373 to prevent symptomatic mild, moderate, or severe COVID-19 in baseline seronegative/PCR-negative adolescent participants were reported in the following subgroups:

- Participants 12 to < 15 years of age: 80.67% (95% CI: 38.47, 93.93)
- Participants 15 to < 18 years of age: 76.76% (95% CI: -26.66, 95.74)
- Male participants: 61.83% (95% CI: -70.48, 91.46)
- Female participants: 86.71% (95% CI: 51.82, 96.33)
- White participants: 78.58% (95% CI: 43.73, 91.84)

- Non-White participants: 100.00% (95% CI: -1930.52, 100.00)
- Mixed origin participants: 100.00% (95% CI: -1886.85, 100.00)
- Hispanic or Latino participants: 100.00% (95% CI: -1937.83, 100.00)
- Not Hispanic or Latino participants: 78.24% (95% CI: 42.85, 91.71)

The VEs for participants 15 to < 18 years of age, male, non-White, mixed origin, and Hispanic or Latino are based on limited numbers and since the lower bound of the 95% CI crosses 0 due to the low number of adolescent participants being part of those subgroups, these do not allow meaningful interpretation.

Parameter	Number of Events[1]/Subgroup		Vaccine Efficacy (95% CI)
	NVX-CoV2373	Placebo	
Final analysis of the primary endpoint	**6/1205 (0.5)**	**14/594 (2.4)**	**79.54 (46.83, 92.13)[2]**
Subgroup: Age			
Participants 12 to < 15 years	4/822 (0.5)	10/407 (2.5)	80.67 (38.47, 93.93)[2]
Participants 15 to < 18 years	2/383 (0.5)	4/187 (2.1)	76.76 (-26.66, 95.74)[2]
Subgroup: Sex			
Male	3/622 (0.5)	4/328 (1.2)	61.83 (-70.48, 91.46)[2]
Female	3/583 (0.5)	10/266 (3.8)	86.71 (51.82, 96.33)[2]
Subgroup: Race (summary)			
White	6/922 (0.7)	13/447 (2.9)	78.58 (43.73, 91.84)[2]
Non-White	0/276 (0)	1/143 (0.7)	100.00 (-1930.52, 100.00)[3]
Subgroup: Race (individual)			
White	6/922 (0.7)	13/447 (2.9)	78.58 (43.73, 91.84)[2]
Black or African American	0/155 (0)	0/77 (0)	NA
American Indian or Alaska Native	0/13 (0)	0/6 (0)	NA
Asian	0/38 (0)	0/26 (0)	NA
Native Hawaiian or Other Pacific Islander	0/3 (0)	0/1 (0)	NA
Mixed origin	0/67 (0)	1/33 (3.0)	100.00 (-1886.85, 100.00)[3]
Subgroup: Ethnicity			
Hispanic or Latino	0/185 (0)	1/100 (1.0)	100.00 (-1937.83, 100.00)[3]
Not Hispanic or Latino	6/1015 (0.6)	13/494 (2.6)	78.24 (42.85, 91.71)[2]

Abbreviations: BMI = body mass index; CI = confidence interval; COVID-19 = coronavirus disease 2019; NVX-CoV2373 = 5 µg SARS-CoV-2 rS with 50 µg Matrix-M1 adjuvant; PCR = polymerase chain reaction; PP-EFF = Per-Protocol Efficacy; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SARS-CoV-2 rS = severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine.
1. Event = PCR-confirmed mild, moderate or severe COVID-19 with onset from 7 days after the second vaccination within the surveillance period.
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] fitted separately to each subgroup.
3. In the event when there were zero cases in either vaccine group or the total number of cases in both vaccine groups combined < 5, VE and 95% CI were estimated with 1 – ratio of incidence rates using the exact method conditional on the total number of cases. NE = not estimable in the event the test for exact binomial proportion cannot be conducted.

Source: T14.2.1.1.2, T14.2.1.1.4.1, T14.2.1.1.4.2, T14.2.1.1.4.3.1, T14.2.1.1.4.3.3, T14.2.1.1.4.4

Summary of main study

The following table summarise the efficacy results from the main studies supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of Efficacy for trial 2019nCoV-301

Title: Phase 3, randomised, placebo controlled study to evaluate the efficacy, safety and immunogenicity of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine (SARS-CoV-2 rS) with Matrix M1 adjuvant: paediatric expansion in adolescents (12 to <18 years).		
Study identifier	2019nCoV-301	
Design	Randomised, placebo controlled, trial. In addition, a non-randomised non-inferiority comparison will be made, bridging adolescent and adult data.	
	Duration of main phase: Duration of Run-in phase:	4 months not applicable

	Duration of Extension phase:		not applicable
Hypothesis	Descriptive, non-inferiority comparisons made.		
Treatments groups	NVX-CoV2373		2 doses 0.5 mL injections of SARS-CoV-2 rS (5 µg) + Matrix-M1 adjuvant (50 µg) given on D0 and D21, n=1491
	Placebo		2 doses 0.5 mL injections normal saline given on D0 and D21, n=756
Endpoints and definitions (no multiplicity control)	Primary immunogenicity endpoint	Neutralising antibodies	Neutralising antibody response at Day 35 for all adolescent participants seronegative to anti-SARSCoV-2 NP antibodies at baseline
	Primary efficacy endpoint	Mild, moderate, severe COVID-19	First episode of PCR-positive mild, moderate, or severe COVID-19, diagnosed ≥D35 in baseline seronegative/ PCR—negative adolescent participants
Database lock	6 October 2021		

Results and Analysis

Analysis description	**Primary Immunogenicity Analysis**		
Analysis population and time point description	PP-IMM analysis set: participants with a baseline and ≥1 serum sample result available after vaccination, no major protocol violations considered clinically relevant to impact immunological measures prior to the visit in question. The PP-IMM Analysis Set also excluded participants who had a PCR-positive nasal swab between baseline up to the visit analysed. Neutralising antibody levels were measured at baseline and Day 35 (14 days after second vaccination).		
Descriptive statistics and estimate variability	Treatment group	Paediatric Expansion (12 to <18 yrs), NVX-CoV2373 group	Adult main study (18 to <26 yrs)
	Number of subjects	390	416
	D0 GMT	10.4	10.3
	95% CI	(10.0, 10.7)	(10.0, 10.5)
	D35 GMT	3860	2634
	95% CI	(3423, 4352)	(2389, 2904)
	Number of subjects	385	415
	D35 Seroconversion (%)	98.7%	99.8%
	95% CI	(97.0, 99.6)	(98.7, 100.0)
Effect estimate per comparison	Co-Primary endpoint	Comparison groups	Adult main study (18 to <26yrs) vs Paediatric expansion (12 to <18 yrs)
		GMR	0.7
		95% CI	(0.6, 0.8)
		P-value	*n.a.*
	Co-Primary	Comparison groups	Adult main study (18 to <26yrs) vs Paediatric expansion (12 to <18 yrs)
		SCR difference (%)	1.1
		95% CI	(-0.2, 2.8)
		P-value	n.a.

Notes	*Whilst a non-randomised, non-inferiority analysis was planned for, this was descriptive in nature and no formal hypothesis testing was planned for. Successful demonstration of NI (primary immunogenicity objective) required meeting 3 pre-specified criteria simultaneously*: *1. Upper bound of 95% CI for GMR (GMT18-<26yo /GMT12-<18yo) < 1.5* *2. Point estimate of GMR ≤ 1.22* *3. Upper bound of 95% CI for ΔSCR (SCR18-<26yo - SCR12-<18yo) < 10%* *All these criteria were met, although no hypothesis testing took place, therefore a formal claim of non-inferiority cannot be made*		
Analysis description	**Primary Efficacy Analysis**		
Analysis population and time point description	PP-EFF, including participants who received the full prescribed regimen of trial vaccine and had no major protocol deviations that occurred before the first COVID-19 positive episode and were determined to affect the efficacy outcomes, including baseline SARS-CoV-2 seropositivity or nasal swab PCR-positivity. Cases were included occurring from Day 35 (14 days after second vaccination) up to receipt of cross over vaccine / DCO		
Descriptive statistics and estimate variability	Treatment group	NVX-CoV2373	Placebo
	Number of subjects	1205	594
	Mild, moderate, severe COVID-19, n (%)	6 (0.5)	14 (2.4)
	Mean disease incidence rate per 100 py	2.90	14.20
	95% CI	1.31, 6.46	8.42, 23.93
Effect estimate per comparison	Co-Primary endpoint	Comparison groups	NVX-CoV2373/Placebo
		Vaccine Efficacy (%)	79.5
		95% CI	46.8, 92.1
		P-value	*n.a.*
Notes	VE was defined as VE (%) = (1 − RR) × 100, where RR = relative risk of incidence rates between the 2 trial vaccine groups (NVX-CoV2373/placebo). Analyses were descriptive.		

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The application is based on the paediatric expansion of 2019nCoV-301, a 2:1 randomised placebo controlled observer blinded trial which is currently ongoing in the US and Mexico. Interim analyses for the adult part of this trial were pivotal in the approval of Nuvaxovid in adults, demonstrating an estimated VE of 90% in context of circulation of the Alpha variant of SARS-CoV-2. No regulatory advice from EU agencies has been obtained for this trial.

All analyses in the paediatric expansion were of a descriptive nature with no hypothesis defined nor tested.

In order to infer efficacy in adolescents, the most relevant objective of primary interest in this assessment is the immunogenicity objective in which the neutralising antibody response is bridged to the clinical efficacy demonstrated in adults. The primary clinical efficacy objective which aims to demonstrate efficacy against COVID-19 is considered of supportive value, mainly as these analyses were not powered for.

Immunobridging was based on the neutralising antibody levels for SARS-CoV-2 wild-type virus as measured 2 weeks after the second dose in a randomly selected subset of baseline seronegative participants. There is currently no serological correlate of protection for COVID-19. However, considering that neutralising antibodies are crucial for protection, immunobridging based on this marker to a population where efficacy has been demonstrated is an accepted strategy for ensuring efficacy in adolescents.

Three criteria were defined which were to be met in order to declare non-inferiority of the neutralising antibody response in adolescents versus adults aged 18 to <26 years (based on the ratio of GMTs at D35 between the two groups as well as based on the seroconversion rate from D0 to D35), however as no formal hypothesis testing was planned, a formal claim of non-inferiority cannot be made.

The case definition and methods for case identification and collection were very much in line with the adult part of 2019nCOV-301 and acceptable. The case definition for severe COVID-19 was adapted to the paediatric population by inclusion of MIS-C which is appropriate. Further the case definition for moderate COVID-19 was also slightly adapted by removing the criteria of having 'fever and 2 COVID-19 symptoms' to classify as a moderate COVID-19 case. This is appropriate.

The main shortcoming of the methods is the lack of planned formal hypothesis testing, while multiple primary endpoints have been defined in various subsets. Considering the selected endpoints, sufficiently large sample size and generally acceptable predefined methods as well as the acceptable conduct of the trial (see below), the descriptive results are sufficient to infer efficacy in adolescents – also considering efficacy in adults has been robustly established and it is anticipated that the immune response at a similar dose will be higher in adolescents compared to adults.

Efficacy data and additional analyses

Overall, the conduct of the trial is acceptable, with relatively few protocol deviations resulting in exclusion from the PP populations. As in the adult part of the trial, a relevant proportion of participants requested unblinding for receipt of an EUA approved vaccine - slightly more often in the placebo group (n=40, 5.3%) compared to the NVX-CoV2373 group (n=60, 4.0%).

The median age of participants was 14 years, with 67% aged between 12 and 15 years of age. The majority of participants was male (52.5%), with relatively more males included in the placebo group (56%) compared to the NVX-CoV2373 group (51%).

Participant ethnicity was mostly 'White' or 'Not Hispanic or 'Latino'; 27% of participants were considered Obese (BMI ≥30) at baseline. In total, 16.1% (n=359) of participants was seropositive (n=348, 15.6%) and/or had a positive (n=21, 0.9%) PCR at baseline.

The baseline characteristics for the cohort of young adults (18-25 years) from the main adult study which formed the comparator group for the non-inferiority analysis showed that the adolescent subset included relatively more males (52.3%) compared to the young adult subset (46.6%). Further, adolescents were less often of Hispanic or Latino ethnicity (16.7% vs. 32.2% in young adults).

Immunobridging

Generally, adolescents have higher immune responses to vaccination compared to adults, which has been shown for e.g. HPV vaccines. This was shown to be the case also for Nuvaxovid vaccine, which is not considered surprising as the adult vaccine dose was also used in adolescents (dose was not reduced for adolescents). The seroresponse rate was non-inferior (99% vs 100%, with a difference of 1.1%, 95% CI: -0.2%, 2.8%) and the GMTs were in fact higher in the adolescent participants (GMT: 3860, 95%CI: 3423, 4352) compared to adult participants aged 18 to <26 (GMT: 2634, 95% CI: 2389, 2904), which was not unexpected. The three predefined NI criteria were met, although no formal testing was undertaken.

The MAH informed that assays are being developed for further evaluation of immunogenicity against variant strains (e.g., Alpha, Beta, and Delta), and that these data may be provided in subsequent reports as available. It is recommended that (i) assays for the Omicron variant are also developed, (ii) if possible, Omicron assays should bracket the antigenic diversity seen in Omicron lineages, and (iii) development of immunogenicity assays based on currently circulating variants of concern should be prioritised, and results reported as soon as possible **(REC)**.

Efficacy

For efficacy, the most relevant objective, i.e. the objective of primary interest to this assessment, is the immunogenicity objective in which the response in adolescents is bridged to the clinical efficacy as demonstrated for adults. The clinical efficacy objective which aims to demonstrate efficacy against COVID-19 is considered of relevance, but although they are stated as primary objective these analyses were only descriptive and not powered for, therefore they are considered of supportive value.

In the adolescent group, in the efficacy analyses of the evaluable efficacy population based on cases reported from at least 14 days after Dose 2 through the data cut-off date, the estimated VE was 79.5% based on 6 (0.5%) and 14 (2.4%) cases in the NVX-CoV2373 and placebo group, respectively, with 2-sided 95% CI: 46.8, 92.1% for individuals without evidence of prior SARS-CoV-2 infection before vaccination. The effect size was in agreement with that seen in adults overall, which was also anticipated based on immunogenicity data.

All cases were mild in severity, with no moderate or severe cases of COVID-19 among participants. Whilst efficacy in adults was estimated at the time of predominance of the Alpha variant, efficacy in adolescents has been estimated at the time of predominance of the Delta variant with all evaluable cases in the study due to Delta.

As there was only one additional COVID-19 case with onset from at least 14 days after second vaccination in participants seropositive at baseline, in the placebo group, the estimated VE in adolescent participants regardless of baseline serostatus (VE = 80.8% [95% CI: 50.5, 92.5]) is similar to the primary efficacy endpoint.

The efficacy analysis for PCR-confirmed symptomatic mild, moderate, or severe COVID-19 with onset from first vaccination in the FAS population included 11 cases (0.7%) in the NVX-CoV2373 group and 18 (2.4%) cases in the placebo group, with an estimated VE of 69.7% (2-sided 95% CI: 36.0, 85.7).

Overall, these efficacy data support the protective efficacy of NVX-CoV2373 in adolescents 12 to <18 years of age.

2.4.3. Conclusions on the clinical efficacy

It can be concluded that NVX-CoV2373 is efficacious in protecting individuals 12 to <18 years of age against symptomatic COVID-19 based on non-inferior immune responses, which is supported by descriptive efficacy analyses.

The following measures are considered necessary to address issues related to efficacy:

- The MAH is recommended to provide data from the assays being developed for further evaluation of immunogenicity against variant strains (e.g., Alpha, Beta, and Delta). The MAH is also recommended to (i) develop immunogenicity assays for the Omicron variant, (ii) if possible, Omicron assays should bracket the antigenic diversity seen in Omicron lineages (as of May 2022, BA.1 through BA.5), and (iii) development of immunogenicity assays based on currently circulating variants of concern should be prioritised, and results reported as soon as possible **(REC)**.

2.5. Clinical safety

Introduction

The safety of Nuvaxovid in adults (median age was 48 years; range 18 to 95 years) was evaluated in pooled data from 5 ongoing clinical trials conducted in Australia, South Africa, the United Kingdom, the United States and Mexico. At the time of the analysis, a total of 49,950 participants aged 18 years and older received at least one dose of Nuvaxovid (n=30,058) or placebo (n=19,892).

The most frequent adverse reactions in adults 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. Further, local and systemic adverse reactions were more frequently reported after Dose 2 than after Dose 1.

Patient exposure

A total of 2,232 adolescent participants received at least 1 dose of NVX-CoV2373 or placebo, with 2,198 (98.5%) receiving both doses of study vaccine.

Median duration of the safety follow-up period after first and second vaccinations were 94 and 71 days, respectively, in the NVX-CoV2373 group and 93 and 71 days, respectively, in the placebo group. Of the 1,468 and 730 participants in the NVX-CoV2373 and placebo groups, respectively, who received both vaccinations, 1,277 (87.0%) and 618 (84.7%), respectively, had at least 60 days of follow-up after their second vaccination.

Adverse events

Solicited reactions

Local reactions dose 1: Following first vaccination in all participants, there was a higher frequency of solicited local TEAEs in the NVX-CoV2373 group (65.4%) than in the placebo group (28.5%). Frequencies of Grade 3 events were low but occurred at a higher frequency in the NVX-CoV2373 group (1.5%) than in the placebo group (0.7%). Tenderness and pain were the most frequent solicited local TEAEs in the NVX-CoV2373 (56.4% and 44.6%, respectively) and placebo (21.1% and 17.4%, respectively) groups. Median duration of tenderness and pain were 2.0 and 2.0 days, respectively, in the NVXCoV2373 group and 1.0 and 1.0 day, respectively, in the placebo group.

Local reactions dose 2: Following second vaccination in all participants, the frequency of solicited local TEAEs in the NVX-CoV2373 group (75.3%) was increased relative to the first vaccination (65.4%) and

remained higher than in the placebo group (20.6%) (Table 17). The intensity of solicited local TEAEs was increased in the NVX-CoV2373 group, as a higher frequency of participants reported Grade 3 events than after Dose 1 (8.5% vs 1.5%, respectively). Injection site tenderness and pain remained the most frequent solicited local TEAEs in the 2 study vaccine groups, 65.2% and 61.0%, respectively, in the NVX-CoV2373 group, and 14.1% and 14.9%, respectively, in the placebo group. Median durations of tenderness and pain were 2.0 and 2.0 days in the NVX-CoV2373 group and 1.0 and 1.0 day in the placebo group.

Table 17. Summary of Solicited Local Adverse Events within 7 Days after Dose 1 and Dose 2 in All Adolescent Participants (Safety Analysis Set)

Solicited Local Adverse Events	NVX-CoV2373 N = 1487	Placebo N = 745
Any local adverse event, N1/N2	**1448/1394**	**726/686**
Dose 1 (any grade)	947 (65.4)	207 (28.5)
Grade 3	22 (1.5)	5 (0.7)
Grade 4	0	0
Dose 2 (any grade)	1050 (75.3)	141 (20.6)
Grade 3	118 (8.5)	4 (0.6)
Grade 4	0	0
Any pain, N1/N2	**1448/1394**	**726/686**
Dose 1 (any grade)	646 (44.6)	126 (17.4)
Grade 3	10 (0.7)	2 (0.3)
Grade 4	0	0
Dose 2 (any grade)	850 (61.0)	102 (14.9)
Grade 3	38 (2.7)	3 (0.4)
Grade 4	0	0
Any tenderness, N1/N2	**1448/1394**	**726/686**
Dose 1 (any grade)	817 (56.4)	153 (21.1)
Grade 3	16 (1.1)	2 (0.3)
Grade 4	0	0
Dose 2 (any grade)	909 (65.2)	97 (14.1)
Grade 3	93 (6.7)	1 (0.1)
Grade 4	0	0
Any erythema, N1/N2	**1448/1394**	**726/686**
Dose 1 (any grade)	15 (1.0)	5 (0.7)
Grade 3	0	0
Grade 4	0	0
Dose 2 (any grade)	104 (7.5)	0
Grade 3	10 (0.7)	0
Grade 4	0	0
Any swelling, N1/N2	**1448/1394**	**726/686**
Dose 1 (any grade)	20 (1.4)	3 (0.4)
Grade 3	0	1 (0.1)
Grade 4	0	0
Dose 2 (any grade)	111 (8.0)	1 (0.1)
Grade 3	8 (0.6)	0
Grade 4	0	0

Abbreviations: N = number of participants in the Safety Analysis Set following Dose 1/Dose 2; N1 = number of participants in the Safety Analysis Set who received the first dose and completed at least 1 day of the reactogenicity diary; N2 = number of participants in the Safety Analysis Set who received the second dose and completed at least 1 day of the reactogenicity diary; NVX-CoV2373 = 5 µg SARS-CoV-2 rS with 50 µg Matrix-M1 adjuvant; SARS-CoV-2 rS = severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine; US FDA = United States Food and Drug Administration. Note: Data are presented as number (%) of participants experiencing a solicited event. Percentages were based on n/N1 × 100 and n/N2 × 100. At each level of participant summarisation, a participant was counted once if they indicated the event occurred and provided a severity during the reactogenicity period. The highest severity experienced during the reactogenicity period is summarised in this table. Note: Grading of solicited adverse events was based on US FDA Toxicity Grading Scale for Clinical Abnormalities (see Appendix 4 of Clinical Protocol 2019nCoV-301) Note: Any grade pertains to reactions reported at grade ≥ 1.
Source: T14.3.2.1.1, T14.3.2.2.1T14.3.2.1.6, T14.3.2.2.6

Systemic reactions dose 1: Following first vaccination in all participants, there was a higher frequency of solicited systemic TEAEs in the NVX-CoV2373 group (55.2%) than in the placebo group (40.8%). Most participants in either treatment group reported events that were of Grade 1 or Grade 2 severity. Frequencies of Grade 3 events were low and occurred at a similar frequency in the NVX-CoV2373 group (3.6%) and in the placebo group (3.4%). Two (0.1%) participants in the NVX-CoV2373 group and none in the placebo group reported Grade 4 fever events. Upon further examination, the Grade 4 fever TEAEs were found to be reported by mistake in the participant-reported eDiary. Muscle pain, headache, fatigue, and malaise were the most frequent solicited systemic TEAEs in the NVX-CoV2373 (34.0%, 30.3%, 24.2%, and 14.8%, respectively) and placebo (15.7%, 24.9%, 15.4%, and 9.2%, respectively) groups; median durations of these events were 1.0 day.

Systemic reactions dose 2: Following second vaccination in all participants, the frequency of solicited systemic TEAEs in the NVX-CoV2373 group (74.5%) increased relative to the first vaccination (55.2%) and remained higher than in the placebo group (28.9%). The intensity of solicited local TEAEs was also increased in the NVX-CoV2373 group, as higher frequencies of participants reported Grade 3 events than after Dose 1 (21.9% vs 3.6%, respectively). There were 2 reports (0.1%) of Grade 4 events in the NVX-CoV2373 group, and none in the placebo group. The 2 Grade 4 TEAEs were one headache and one nausea/vomiting. The Grade 4 TEAE of headache qualified as such based on the participant visit to the emergency room (ER) and had a duration of 1 day. The Grade 4 TEAE of nausea/vomiting was found to be part of an AE of gastroenteritis that the participant experienced and that prompted an ER visit, however, the symptom was nonetheless reported with a duration of 1 day. Headache, fatigue, muscle pain, and malaise remained the most frequent solicited systemic TEAEs in the 2 treatment groups, with median durations remaining at 1.0 day, except for muscle pain in the NVX-CoV2373 group where it was 2.0 days.

Table 18. Summary of Solicited Systemic Adverse Events within 7 Days after Dose 1 and Dose 2 in All Adolescent Participants (Safety Analysis Set)

Solicited Systemic Adverse Events	NVX-CoV2373 N = 1487	Placebo N = 745
Any solicited systemic TEAE, N1/N2	**1448/1394**	**726/686**
Dose 1 (any grade)	799 (55.2)	296 (40.8)
Grade 3	52 (3.6)	25 (3.4)
Grade 4	2 (0.1)	0
Dose 2 (any grade)	1038 (74.5)	198 (28.9)
Grade 3	305 (21.9)	23 (3.4)
Grade 4	2 (0.1)	0
Headache, N1/N2	**1448/1394**	**726/686**
Dose 1 (any grade)	439 (30.3)	181 (24.9)
Grade 3	13 (0.9)	12 (1.7)
Grade 4	0	0
Dose 2 (any grade)	793 (56.9)	119 (17.3)
Grade 3	87 (6.2)	14 (2.0)
Grade 4	1 (< 0.1)	0
Fatigue, N1/N2	**1448/1394**	**726/686**
Dose 1 (any grade)	350 (24.2)	112 (15.4)
Grade 3	23 (1.6)	9 (1.2)
Grade 4	0	0
Dose 2 (any grade)	695 (49.9)	100 (14.6)
Grade 3	185 (13.3)	10 (1.5)
Grade 4	0	0
Malaise, N1/N2	**1448/1394**	**726/686**
Dose 1 (any grade)	215 (14.8)	67 (9.2)
Grade 3	16 (1.1)	7 (1.0)
Grade 4	0	0
Dose 2 (any grade)	560 (40.2)	51 (7.4)
Grade 3	126 (9.0)	4 (0.6)
Grade 4	0	0
Muscle pain, N1/N2	**1448/1394**	**726/686**
Dose 1 (any grade)	492 (34.0)	114 (15.7)
Grade 3	17 (1.2)	4 (0.6)
Grade 4	0	0
Dose 2 (any grade)	683 (49.0)	82 (12.0)
Grade 3	104 (7.5)	6 (0.9)
Grade 4	0	0
Joint pain, N1/N2	**1448/1394**	**726/686**
Dose 1 (any grade)	101 (7.0)	35 (4.8)
Grade 3	6 (0.4)	1 (0.1)
Grade 4	0	0
Dose 2 (any grade)	225 (16.1)	21 (3.1)
Grade 3	40 (2.9)	2 (0.3)
Grade 4	0	0
Fever, N1/N2	**1448/1394**	**726/686**
Dose 1 (any grade)	10 (0.7)	4 (0.6)
Grade 3	1 (< 0.1)	0
Grade 4	2 (0.1)	0
Dose 2 (any grade)	235 (16.9)	1 (0.1)
Grade 3	31 (2.2)	0
Grade 4	0	0

Solicited Systemic Adverse Events	NVX-CoV2373 N = 1487	Placebo N = 745
Nausea/Vomiting, N1/N2	**1448/1394**	**726/686**
Dose 1 (any grade)	112 (7.7)	54 (7.4)
Grade 3	2 (0.1)	3 (0.4)
Grade 4	0	0
Dose 2 (any grade)	277 (19.9)	33 (4.8)
Grade 3	14 (1.0)	3 (0.4)
Grade 4	1 (< 0.1)	0

Abbreviations: N = number of participants in the Safety Analysis Set following Dose 1/Dose 2; N1 = number of participants in the Safety Analysis Set who received the first dose and completed at least 1 day of the reactogenicity diary; N2 = number of participants in the Safety Analysis Set who received the second dose and completed at least 1 day of the reactogenicity diary; NVX-CoV2373 = 5 µg SARS-CoV-2 rS with 50 µg Matrix-M1 adjuvant; SARS-CoV-2 rS = severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine; US FDA = United States Food and Drug Administration.
Note: Data are presented as number (%) of participants experiencing a solicited event. Percentages were based on n/N1 × 100 and n/N2 × 100. At each level of participant summarisation, a participant was counted once if they indicated the event occurred and provided a severity during the reactogenicity period. The highest severity experienced during the reactogenicity period is summarised in this table.
Note: Grading of solicited adverse events was based on US FDA Toxicity Grading Scale for Clinical Abnormalities (see Appendix 4 of Clinical Protocol 2019nCoV-301). Note: Any grade pertains to reactions reported at grade ≥ 1. Source: T14.3.2.1.1, T14.3.2.2.1T14.3.2.1.6, T14.3.2.2.6

Unsolicited TEAEs

Unsolicited TEAEs with onset from after Dose 1 through the data cut off or administration of crossover vaccination occurred at similar frequencies in the NVX-CoV2373 group and in the placebo group (n=243, 16.3% and n=118, 15.8%, respectively). Severe TEAEs were reported in 6 (0.4%) participants in the NVX-CoV2373 group and 2 (0.3%) participants in the placebo group. Most TEAEs occurred within 49 days after first vaccination (n=241, 16.2% and n=117, 15.7%, in the NVX-CoV2373 group and in the placebo group respectively).

TEAEs of the SOCs Infections and Infestations, Respiratory, Thoracic and Mediastinal Disorders, General Disorders and Administration Site Conditions, Injury, Poisoning and Procedural Complications, and Nervous System Disorders were the most frequent (incidence > 2.0% in the NVX-CoV2373 group) in adolescent participants 12 to < 18 years of age. The most frequent TEAEs (incidence > 1.0%) were nasal congestion, headache, cough, and oropharyngeal pain in the NVX-CoV2373 group and upper respiratory tract infection, oropharyngeal pain, nasal congestion, headache, and rhinorrhoea in the placebo group.

Unsolicited Treatment-Related TEAEs

Among adolescent participants 12 to < 18 years of age, unsolicited treatment-related TEAEs from first vaccination to Day 49 occurred with a higher frequency of participants reporting them in the NVX-CoV2373 group (3.4%) than in the placebo group (1.1%). This difference was largely due to treatment-related TEAEs in the SOC General Disorders and Administration Site Conditions (1.6% vs 0.1%, respectively), where the most frequent TEAEs of chills, fatigue, injection site pain, and pyrexia only occurred in the NVX-CoV2373 group, and the SOC Nervous System Disorders, where the TEAE of headache was the most frequently reported. Most of these terms were related to solicited vaccine reactogenicity that were counted as treatment-related TEAEs as well. The most frequent treatment-related TEAE overall was lymphadenopathy, which only occurred in the NVX-CoV2373 group.

AESIs

There were no Potential Immune-Mediated Medical Conditions (PIMMCs) reported in the paediatric expansion. There was on Adverse Event of Special Interest. There were 5 (0.3%) participants in the NVX-CoV2373 group and 5 (0.7%) participants in the placebo group who reported COVID-19-related TEAEs in the paediatric expansion; al were mild.

Serious adverse event/deaths/other significant events

There were no deaths among the adolescent participants in the paediatric expansion at the time of this data extraction.

SAEs were reported by <1% of participants in each treatment group. There was a numerically higher frequency of participants reporting unsolicited SAEs in the NVX-CoV2373 group (n = 7, 0.5%) than in the placebo group (n = 2, 0.3%). Unsolicited SAEs in the SOCs Injury, Poisoning and Procedural Complications, Infections and Infestations, and Psychiatric Disorders were the most frequent (incidence > 2 participants across both treatment groups). Only 1 SAE ([redacted]) was reported in 2

participants (both in the NVX-CoV2373 group). All SAEs were assessed by the investigator as not related to study treatment.

Table 19. Overall Summary of Unsolicited Serious Adverse Events From Start of First Vaccination to Blinded Crossover Dose in All Adolescent Participants in any Study Vaccine Group by Age Strata (Safety Analysis Set)

System Organ Class/ Preferred Term (MedDRA, Version 23.1)	Participants 12 to < 18 Years		Participants 12 to < 15 Years		Participants 15 to < 18 Years	
	NVX-CoV2373 N = 1487	Placebo N = 745	NVX-CoV2373 N = 998	Placebo N = 500	NVX-CoV2373 N = 489	Placebo N = 245
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any system organ class	**7 (0.5)**	**2 (0.3)**	**5 (0.5)**	**1 (0.2)**	**2 (0.4)**	**1 (0.4)**
Injury, poisoning and procedural complications	**3 (0.2)**	**0**	**2 (0.2)**	**0**	**1 (0.2)**	**0**
[redacted]	2 (0.1)	0	1 (0.1)	0	1 (0.2)	0
	1 (< 0.1)	0	1 (0.1)	0	0	0
Infections and infestations	**2 (0.1)**	**1 (0.1)**	**1 (0.1)**	**0**	**1 (0.2)**	**1 (0.4)**
Gastroenteritis norovirus	1 (< 0.1)	0	0	0	1 (0.2)	0
Localised infection	1 (< 0.1)	0	1 (0.1)	0	0	0
Peritonsillar abscess	0	1 (0.1)	0	0	0	1 (0.4)
Nervous system disorders	**2 (0.1)**	**0**	**1 (0.1)**	**0**	**1 (0.2)**	**0**
Juvenile myoclonic epilepsy	1 (< 0.1)	0	1 (0.1)	0	0	0
Seizure	1 (< 0.1)	0	0	0	1 (0.2)	0
Psychiatric disorders	**2 (0.1)**	**1 (0.1)**	**2 (0.2)**	**1 (0.2)**	**0**	**0**
[redacted]	1 (< 0.1)	0	1 (0.1)	0	0	0
	1 (< 0.1)	0	1 (0.1)	0	0	0
	0	1 (0.1)	0	1 (0.2)	0	0

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; NVX-CoV2373 = 5 µg SARS-CoV-2 rS with 50 µg Matrix-M1 adjuvant; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SARS-CoV-2 rS = severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine. Source: T.14.3.4.9.1, T14.3.4.9.2

Laboratory findings

No scheduled laboratory assessments for safety were implemented in the study.

Safety in special populations

The MAH conducted several subgroup analyses to evaluate the impact on vaccine safety.

• Frequencies and intensities of solicited systemic TEAEs among NVX-CoV2373 recipients after each vaccination were similar among each age subgroup (12 to < 15 years and 15 to < 18 years).

• Male participants reported lower frequencies and intensities of solicited systemic TEAEs among both NVX-CoV2373 and placebo recipients after each vaccination than in female participants.

• Black or African American and American Indian or Alaska Native participants reported lower frequencies and intensities of solicited systemic TEAEs among NVX-CoV2373 recipients after each vaccination than in participants of other races.

• There were generally similar frequencies and intensities of solicited systemic TEAEs after each vaccination among White, Asian, and mixed origin race participants in the NVX-CoV2373 group. Native Hawaiian/Other Pacific Islander was the only group with increased frequency of solicited systemic TEAEs among all races, but the number of participants in this category is too low to allow for meaningful interpretation.

• Hispanic or Latino participants reported lower frequencies of solicited systemic TEAEs among both NVX-CoV2373 and placebo recipients after each vaccination than in not Hispanic or Latino participants. Severity (based on percentage of participants with Grade 3+ systemic TEAEs), however, is similar among the 2 ethnic groups.

Safety related to drug-drug interactions and other interactions

Drug-drug interactions were not evaluated in this study.

Discontinuation due to adverse events

There were no TEAEs reported that led to study discontinuation in any adolescent participant.

Unsolicited TEAEs resulting in study vaccine discontinuation were reported in 1 participant each in the NVX-CoV2373 and placebo groups. A TEAE of juvenile myoclonic epilepsy was reported by a participant in the NVX-CoV2373 group (see section on SAEs) and a TEAE of rhinorrhoea was reported in the placebo group; both events occurred in participants 12 to < 15 years of age and both were assessed by the investigator as not related to study treatment.

One additional participant in the NVX-CoV2373 group reported a TEAE of headache that resulted in discontinuation of study vaccine, this event was a solicited TEAE that continued beyond the 7-day reactogenicity period.

Post-marketing experience

Nuvaxovid received a conditional marketing authorisation in the European Union (EU) on 20 December 2021. According to the latest MSSR (17 March 2022), there are no safety updates for Nuvaxovid. By 28 February 2022, the vaccine was not yet in use in the EU/EEA.

2.5.1. Discussion on clinical safety

This application concerns adolescents 12 to <18 years of age which have subsequently been recruited to the paediatric expansion of ongoing phase 3 trial 2019nCoV-301 which was pivotal for the approval in adults. The same dose of NVX-CoV2373 as in adults (5-µg dose of SARS-CoV-2 rS with 50 µg Matrix-M adjuvant) has been administered to the adolescents, given as a 2-dose regimen with a 21 day interval.

Up to the cut-off date (6 October 2021), a total of 2,232 adolescents (NVX-CoV2373 n=1,487; placebo n=745) aged 12 to <18 years have been included in the safety population; of these 2,198 (98.5%) received the second dose. The majority of adolescents (67%) were aged 12 to <15 years. Slightly more male participants were included (52.5%). The adolescents were recruited from the USA only. The included numbers of participants are considered sufficient to evaluate the reactogenicity profile in adolescents that receive two doses of NVX-CoV2373. It will however not be possible within this study to detect rare adverse reactions. The safety follow up is considered sufficient, with the median duration of follow up after the second dose of NVX-CoV2373 of 71 days and 1,277 adolescents (87.0%) having at least 60 days of follow up.

Reactogenicity: Tenderness and pain at the injection site was the most frequently reported local reaction in adolescents (56%/47% dose1; 65%/61% dose2), which was significantly higher compared to placebo (21%/17% dose1; 14%/15% dose2).

The most commonly reported solicited systemic TEAEs among the adolescent subjects that received NVX-CoV2373 after the first dose were muscle pain, headache, fatigue, and malaise in the NVX-CoV2373 (34.0%, 30.3%, 24.2%, and 14.8%, respectively) and placebo (15.7%, 24.9%, 15.4%, and 9.2%, respectively) groups; median durations of these events were 1.0 day. Headache, fatigue, muscle pain, and malaise remained the most frequent solicited systemic TEAEs after the second dose, reported by 57.0%, 49.9%, 49.1% and 40.2% in the NVX-CoV2373 group and by 17.3%, 14.6%, 12.0% and 7.4% in the placebo group respectively.

Most of the local and systemic events were mild to moderate in intensity and resolved within 2 days. There were few reports of Grade 4 fever; according to the MAH, reported TEAEs of Grade 4 fever after the first dose were made by mistake. The MAH provided very little detail on the data entries for Grade 4 events which were judged to be reporting mistakes. The MAH confirmed that less severe events (Grade1-3) were not checked with the same thoroughness, therefore the possibility of the presence of data entry errors cannot be excluded. Based on the assumption that errors were made just as often in the placebo as active comparison group, this will unlikely affect overall conclusions.

Generally, the reactogenicity profile in adolescents 12 - < 18 years is similar as that in adults as observed in the same trial, 2019nCoV-301: after the first dose 66% of adolescents reported a local reaction compared to 58% of adults, after the second dose this was 76% compared to 79% respectively. Systemic reactions were also similar; after the first dose these were reported by 55% of adolescents compared to 48% of adults, after the second dose by 75% of adolescents and 70% of adults. The only exception is fever, which was reported more frequently by adolescents: 1% after the first dose, 17% after the second dose (2% grade 3), compared with 0.4% of adults after dose 1 and 6% of adults after dose 2 (0.4% grade 3). The frequency of fever increases with decreasing age, as for adolescents 12-15 years 18% reported fever after the second dose compared with 14% of adolescents aged 16-18 years. In adolescents the median duration of fever after the first and second dose was 1 day, with a maximum duration of 2 days observed after the second dose. The higher fever rates in adolescents are noted in section 4.8 of the SmPC.

Unsolicited AEs with onset from after Dose 1 through to the cut-off date occurred at similar frequencies in the NVX-CoV2373 group and in the placebo group (n=243, 16.3% and n=118, 15.8%, respectively). This was similar as observed in the adult part of 2019nCoV-301 (16.3% vs 14.8%). The most frequent TEAEs (incidence > 1.0%) were nasal congestion, headache, cough, and oropharyngeal pain in the NVX-CoV2373 group and upper respiratory tract infection, oropharyngeal pain, nasal congestion, headache, and rhinorrhoea in the placebo group.

There was a slight imbalance in AEs in the SOC of Eye disorders, (7 (0.5%) vs 1 (0.1%); IR 3.3/100 PY vs 1.0/100 PY), as was observed in adults. Also, as in adults, it was not due to an imbalance related to one specific PT and there is no clear indication of relatedness to the vaccine. As this is already being followed in PSURs/MSSRs no additional action is warranted at this moment

Unsolicited treatment-related AEs from first vaccination to Day 49 occurred with a higher frequency of participants reporting them in the NVX-CoV2373 group (3.4%) than in the placebo group (1.1%). This difference was largely due to the SOC General Disorders and Administration Site Conditions (1.6% vs 0.1%; chills, fatigue, injection site pain, and pyrexia) and the SOC Nervous System Disorders (headache). The most frequent treatment-related TEAE overall was lymphadenopathy, which only occurred in the NVX-CoV2373 group and is already listed in the SmPC.
Clinical laboratory testing was not performed as part of the safety evaluation in adolescents. Considering that there is no need for any clinical laboratory testing to characterise the safety per se, as there is sufficient evidence in adults, the absence of such data is acceptable.

There were no deaths the adolescent participants in the paediatric expansion, nor any serious AEs considered related to NVX-CoV2373. Whilst in the study in adults few cases of pericarditis/myocarditis had been observed following vaccination with NVX-CoV2373, none were observed in the paediatric expansion. However, the study is not large enough to detect rare adverse reactions.

With regards to the SAE of juvenile myoclonic epilepsy resulting in discontinuation of vaccination, it is not entirely clear how far the subject was in neurological diagnostic work-up or when exactly carbamazepine was started and whilst the investigator ruled out possible relatedness due to the reporting of symptoms suggesting seizure activity preceding the date of vaccination, details are too limited to firmly rule out any

role of NVX-CoV2373. However, based on the available information around this single event no conclusions can be drawn and no further action is warranted.

2.5.2. Conclusions on clinical safety

The safety evaluation is based on a paediatric expansion in an ongoing phase 3 study that has included 2,232 adolescents aged 12 to <18 years. The same dose and dose regimen as for the adult population has been used. Overall, the reported reactogenicity profile is in line with what was observed in the adult population, even though a higher frequency of fever was noted in adolescents which is reflected in the SmPC. The reactogenicity profile is considered acceptable. The frequency of reported AEs and SAEs were low. The sample size does not allow detection of rare adverse reactions.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports 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.

2.6. Risk management plan

The MAH submitted/was requested to submit an updated RMP version 1.1 with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 1.1 is acceptable.

The CHMP endorsed this advice without changes.

Safety concerns

The safety profile of NVX-CoV2373 in adolescents aged 12 to 18 years did not reveal any new safety concerns; there were no cases of myocarditis. The safety profile was in line with the current experience in adults. Therefore, it is agreed that the safety specifications remain unchanged.

Myocarditis and pericarditis and are listed as an important potential risk in the EU-RMP of Nuvaxovid following evaluation of the clinical trial data supporting the initial CMA (refer to EPAR). No cases of myocarditis and pericarditis have been reported in the clinical trials supporting this extension of the indication in adolescents.Importantly, reports of myocarditis and pericarditis following Nuvaxovid have been reported in the post-marketing setting and are being closely evaluated by PRAC in the context of the Summary Safety Reports.

The risk of anaphylaxis has been removed from the list of safety concerns, as requested by PRAC. This risk is well known in clinical practice and within the vaccination campaigns in the Member States. Based on the current post marketing experience, the conclusion at approval that routine risk minimisation is sufficient to mitigate this risk is maintained. It is also no longer considered in need of further characterisation within the ongoing PASS programs. Taken together, while anaphylaxis remains a potential risk for the product, as with any other biologicals, it does not have an impact on the benefit / risk balance of the vaccine. Therefore, it is agreed that anaphylaxis is reclassified as not "important" and removed from the summary of safety concerns in the RMP. This event is expected to be monitored via routine pharmacovigilance.

Table 20. Summary of safety concerns

Important identified risks	None
Important potential risks	Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) Myocarditis and pericarditis
Missing information	Use in pregnancy and while breastfeeding Use in immunocompromised patients Use in frail patients with comorbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders Interaction with other vaccines Long-term safety

Pharmacovigilance plan

Table 21. Ongoing and planned additional pharmacovigilance activities

Study/Status	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Not applicable.				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable.				
Category 3 – Required additional pharmacovigilance activities				
Study 2019nCoV-101 (Part 1) Ongoing	To evaluate the safety and immunogenicity of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine (SARS-CoV-2 rS) with or without Matrix-M adjuvant in healthy subjects.	Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) Myocarditis and pericarditis Long-term safety	Final CSR	31 March 2022
Study 2019nCoV-101 (Part 2) Ongoing	To identify the optimal dose across age strata based on immune response (IgG antibody to SARS-CoV-2 rS) at Day 35 and whether baseline immune status has an impact.	Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)	Final CSR	31 December 2022

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	To accumulate a safety experience for the candidate vaccine in healthy adult participants based on solicited short-term reactogenicity across a broad age spectrum (by toxicity grade) and by AE profile for primary vaccination (through Day 35). Identify dose(s) to potentially take forward in an EUA setting and/or for Phase 3 efficacy or effectiveness trial(s).	Myocarditis and pericarditis Long-term safety		
Study 2019nCoV-501 Ongoing	To evaluate the efficacy, immunogenicity, and safety of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine (SARS-CoV-2 rS) with Matrix-M adjuvant in South African adult subjects living without HIV; and safety and immunogenicity in adults living with HIV.	Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) Myocarditis and pericarditis Use in immunocompromised patients Long-term safety	Final CSR	31 December 2022
Study 2019nCoV-302 Ongoing	To evaluate the efficacy and safety of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine (SARS-CoV-2 rS) with Matrix-M adjuvant in adult participants 18-84 years of age in the UK.	Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) Myocarditis and pericarditis Use in immunocompromised patients Interaction with other vaccines Long-term safety	Final CSR	31 December 2022
Study 2019nCoV-301 Ongoing	To evaluate the efficacy, safety, and immunogenicity of a SARS-CoV-2 recombinant spike protein nanoparticle	Vaccine-associated enhanced disease (VAED), including vaccine-associated	Final CSR	30 September 2023

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	vaccine (SARS-CoV-2 rS) with Matrix-M adjuvant in adult participants ≥ 18 years of age with a paediatric expansion study in paediatric participants (12 to < 18 years of age).	enhanced respiratory disease (VAERD) Myocarditis and pericarditis Use in immunocompromised patients Use in patients with autoimmune or inflammatory disorders Long-term safety		
Study 2019nCoV-402 UK Post-Authorisation Safety Study Using the Clinical Practice Research Datalink (CPRD) Planned	• Evaluate any increased risk of select safety outcomes of interest following vaccination. • Describe and characterise the safety profile of Nuvaxovid. • Evaluate any differences in the risk of safety outcomes by characteristics such as age, sex, race/ethnicity, comorbidities/coinfections, prior COVID-19 infection, concomitant vaccinations, concomitant medications, and/or other characteristics.	Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) Myocarditis and pericarditis Use in immunocompromised patients Use in frail patients with co-morbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders Interaction with other vaccines Long-term safety	Protocol submission	31 March 2022
			Progress reports	30 June 2023 and 30 June 2024
			Final study report	30 June 2025

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Study 2019nCoV-405 Global Safety Surveillance Study of Pregnancy and Infant Outcomes Study Using C-VIPER Planned	• Describe and characterise the population of pregnant women who are vaccinated with Nuvaxovid. • Estimate the frequency of select adverse pregnancy outcomes • Estimate the frequency of select adverse foetal/neonatal/infant outcomes at birth and up to the first 12 months of life • Compare the frequency of each safety event of interest between pregnant women (or infants born to these pregnancies) who were exposed to Nuvaxovid and those who were not exposed. • Assess whether the frequency of pregnancy and infant outcomes following vaccination with Nuvaxovid differs by age, sex, race/ethnicity, comorbidities/coinfections, prior COVID-19 infection, concomitant vaccinations, concomitant medications, and/or other characteristics.	Use in pregnancy and while breastfeeding	Protocol submission	31 March 2022
			Progress reports	30 June 2023, 30 June 2024, 30 June 2025, 30 June 2026
			Final study report	30 June 2027
Study 2019nCoV-404 US Post-authorization safety study using a claims and/or EHR database Planned	• To evaluate the pooled risk of select AESIs within specified time periods after vaccination with the Novavax COVID-19 vaccine, compared to risk during all other times after COVID-19 vaccination within the same individual (self-controlled design), or compared to unvaccinated individuals or those	Vaccine-associated enhanced disease (VAED), including vaccine-associated	Protocol submission	30 June 2022
			Progress reports	30 September 2023, 30 September 2024
			Final study report	30 September 2025

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	who received an alternative COVID-19 vaccine (comparative cohort study design) • To evaluate whether the risk of AESIs following vaccination with the Novavax COVID-19 vaccine differs by vaccine dose and characteristics such as age, sex, race/ethnicity, comorbidities/coinfections, prior SARS-CoV-2 infection, concomitant vaccinations, concomitant medications, and/or other characteristics.	enhanced respiratory disease (VAERD) Myocarditis and pericarditis Use in immunocompromised patients Use in frail patients with co-morbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders Interaction with other vaccines Long-term safety		

Table 22. Planned effectiveness studies (required additional pharmacovigilance activities)

Study/Status	Summary of objectives	Effectiveness uncertainties addressed	Milestones	Due dates
Study 2019nCoV-401 EU/EEA Post-Authorisation Effectiveness Study Based on a Test-Negative Design Using the COVIDRIVE Platform Planned	• Estimate the effectiveness of Nuvaxovid against COVID-19 hospitalisations confirmed by RT-PCR, after adjusting for potential confounders • Estimate the effectiveness against COVID-19 hospitalisations stratified by specific populations of interest (e.g., age groups, underlying chronic conditions, COVID-19 risk factors, immunocompromised), after adjusting for potential confounders	COVID-19 vaccine effectiveness in real-world setting	Protocol submission	30 April 2022
			Progress reports	31 January 2023, 31 July 2023, 31 January 2024, 31 July 2024
			Final report	31 January 2025

Study/Status	Summary of objectives	Effectiveness uncertainties addressed	Milestones	Due dates
	• Estimate the effectiveness against COVID-19 hospitalisations stratified by SARS-CoV-2 variants to the extent such data are available			
Study 2019nCoV-403 US Post-authorization Effectiveness Study Using a Claims and/or EHR Database Planned	• To assess the effectiveness of the Novavax COVID-19 vaccine in reducing clinically defined SARS-CoV-2 infection. • To assess the effectiveness of the Novavax COVID-19 vaccine in reducing clinically defined severe SARS-CoV-2 infection • To assess the effectiveness of a single dose of the Novavax COVID-19 vaccine in reducing clinically defined SARS-CoV-2 infection. • To assess the effectiveness of the Novavax COVID-19 vaccine against SARS-CoV-2 variants (where data are available) • To assess the effectiveness of the Novavax COVID-19 vaccine by subgroups e.g., age, sex, race/ethnicity, comorbidities/coinfections, prior SARS-CoV-2 infection, concomitant vaccinations, concomitant medications, and/or other characteristics.	COVID-19 vaccine effectiveness in real-world setting	Protocol submission	30 June 2022
			Progress reports	30 September 2023, 30 September 2024
			Final report	30 September 2025

The MAH was requested to confirm that at all post authorisation safety studies (PASS) and effectiveness studies are extended in order to include adolescents 12 to 17 years of age. The MAH has committed to amend the study protocols of the following studies: 2019nCoV-401, 2019nCoV-402, 2019nCoV-403 and

2019nCoV-404 to include adolescents 12 to 17 years of age upon receipt of the authorisation for this age group. It is acknowledged that study Study 2019nCoV-405 is a pregnancy registry in adults and requires that participants be 18 years of age or older and will not include adolescents.

Risk minimisation measures

Table 23. Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Important identified risks	
None	Not applicable
Important potential risks	
Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None
Myocarditis and pericarditis	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None
Missing information	
Use in pregnancy and while breastfeeding	Routine risk communication: SmPC section 4.6 and 5.3 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None
Use in immunocompromised patients	Routine risk communication: SmPC Section 4.4 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information:

Safety concern	Routine risk minimisation activities
	None
Use in frail patients with comorbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None
Use in patients with autoimmune or inflammatory disorders	Routine risk communication: PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None
Interaction with other vaccines	Routine risk communication: SmPC Sections 4.5 and 5.1 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None
Long-term safety	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, and 5.1 of the SmPC are updated to extend the indication to individuals 12 years of age and older. The Package Leaflet is updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

There is no change proposed in the technical specifications of the package information leaflet. The final report of the PL user testing, which was performed in January 2022, was submitted and evaluated by the EMA within the variation EMEA/H/C/005808/IB/0005, which was approved on 18 March 2022. The changes performed in the PL within the frame of this indication extension variation are minimal. The information is not moved within the document and no new, significantly complex, text constructions are included.

The proposed changes in the PL with respect to currently submitted variation, do not impact the technical readability, comprehensibility of the text, traceability of information, particularly key safety messages, which were investigated in the recently performed and approved user testing. The results of the user testing of the PL approved in December 2021, which were satisfactory and met the success criteria established in the European guideline, are still valid and applicable to the proposed update of the PL. Therefore, performing a new user testing of the proposed package information leaflet, which is submitted within the variation, the adolescent indication extension, is not required.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

COVID-19 is the disease caused by a novel coronavirus, severe acute respiratory coronavirus 2 (SARS-CoV-2). COVID-19 is primarily recognised as febrile respiratory illness. While the majority of cases subsides without specific treatment in a subgroup of patients the disease progresses to severe disease characterised by oxygen requirement. Still fewer patients progress to critical disease with respiratory failure, ARDS, multiorgan failure and/or thromboembolic complications. Age is the major risk factor for severe COVID-19 and death, other described risk factors are obesity, pre-existent diabetes, cardiovascular disease, lung disease, immuno-deficiency and pregnancy. COVID-19 can be considered confirmed by the existence of above clinical signs and proof of the presence of the virus e.g. by NAAT.

In adolescents SARS-CoV-2 infections cause mostly asymptomatic or mild disease. Severe COVID-19 cases occur rarely, and predominantly in subjects with comorbidities.

3.1.2. Available therapies and unmet medical need

To date, several vaccines have been authorised in multiple countries globally for the prevention of COVID-19. Within the EU, five SARS-CoV-2 vaccines are currently authorised; of these, two are authorised for use in adolescents.

Despite available preventative measures and treatments, there remains an unmet medical need. Especially protection of particularly vulnerable groups and mitigating the effects of the pandemic on a population level are desired. While two vaccines for the prevention of COVID-19 are authorised for use in adolescents, there is a likely need for additional vaccines to meet sustained demand and to successfully protect the global community from SARS-CoV-2.

3.1.3. Main clinical studies

This submission is based on one clinical trial conducted in adolescents, a paediatric expansion of study 2019nCoV-301, a randomised (2:1) placebo controlled observer blinded trial of which the adult part was pivotal to the approval of Nuvaxovid in adults.

Vaccine efficacy is inferred based on demonstrating non-inferiority of the geometric mean value of serum neutralising antibodies and the seroresponse rate from adolescent participants (12 to <18 years) compared with those obtained from young adults (18 to <26 years of age) enrolled in the adult part of 2019nCoV-301. Additionally, co-primary endpoints evaluated the effects of Nuvaxovid on COVID-19 as well as the safety of Nuvaxovid in adolescents.

3.2. Favourable effects

Based on *in vitro* and *in vivo* studies it has been demonstrated that neutralising antibodies play a crucial role in preventing COVID-19. Nuvaxovid was shown to elicit non-inferior neutralising antibody levels and seroresponse rates in subjects 12 to <18 years of age without previous SARS-CoV-2 infection compared to young adults 18 to <26 years of age. Based on these immunobridging results efficacy can be inferred for adolescents.

In addition, descriptive analyses of efficacy confirmed protection of Nuvaxovid against COVID-19, with an estimated vaccine efficacy (VE) of 79.5% (95% CI: 46.8%, 92.1%) based on 20 accrued cases (6 in the NVX-CoV2373 group and 14 in the placebo group) found in context of dominant circulation of the Delta variant of the SARS-CoV-2 virus in the US. All of the 11 cases that could be sequenced were Delta variants. Overall, the VE results are consistent with the VE reported in older age groups.

3.3. Uncertainties and limitations about favourable effects

No data are available from adolescents with a risk of more severe disease, including those with comorbidities such as diabetes or those under immune suppressive therapy. A study in immunocompromised children is included in the PIP.

It is currently unknown how long protection will last in adolescents and adults and whether vaccination provides protection against currently dominant variants (i.e. Omicron BA1/BA2) or newly emerging variants.

The impact on transmission is currently unknown.

3.4. Unfavourable effects

The safety of Nuvaxovid administered to adolescent subjects was evaluated in 2,232 participants aged 12 to <18 years of the ongoing phase 3 trial 2019nCoV-301.

As in adults, the safety profile of Nuvaxovid in adolescents is characterised by its reactogenicity. The most frequent reactions were injection site tenderness (56% D1/65% D2) and injection site pain (45% D1/61% D2), headache (30% D1/ 57% D2), fatigue (24% D1/50% D2), muscle pain (34% D1/49% D2) and malaise (15% D1/ 40% D2). Reactogenicity increased with the second dose both in reporting frequency as in severity. The median duration of local and systemic events was 1 to 2 days and reactions were mostly mild to moderate at intensity. The reactogenicity profile is similar to what has been reported in adults, with the exception of fever which occurred at a higher frequency (1% D1/17% D2 vs 0.4% D1/6% D2 in adults)) and was more often severe in adolescent participants, in particular following the second dose (2% grade 3 vs 0.4% grade 3 in adults).

The frequency of AEs and SAEs was in general low and no new safety concerns have been detected compared to what was reported for the adult population. Several events of lymphadenopathy (NVX-CoV2373 0.7% (10 cases); placebo 0% (0 cases)) have been reported.

3.5. Uncertainties and limitations about unfavourable effects

There is a limited number of adolescent subjects aged 12 to <18 years included in the study, which does not allow detection of rare adverse events.

The trial was restricted to healthy and medically stable adolescents. No safety data are available for adolescents with underlying chronic medical conditions and/or immune suppression.

Concomitant use of Nuvaxovid and any other vaccine or any other medication was not evaluated.

3.6. Effects Table

Table 24. Effects Table for Nuvaxovid indicated for adolescents from 12 years onwards (data cut-off: 06 October 2021)

Effect	Short Description	**Unit**	**Treatment**	**Control**	Uncertainties/ Strength of evidence	**References**
Favourable Effects						
Immunogenicity			**12-<18y N=390**	**18-<26y N=416**		
	GMT (95% CI)		3860 (3423, 4352)	2634 (2389, 2904)		
	Neutralising antibody (nAb) titer Ratio older vs younger age group	GMR (95% CI)	**0.7** (0.6, 0.8)		*Non-inferiority demonstrated convincingly*	
	Seroconversion (SCR) rate		98.7% (97.0, 99.6)	99.8% (98.7, 100.0)		
	Difference in nAb SCR rate older vs younger group at day 35 (95% CI)	SCR difference (%)	**1.1** (-0.2, 2.8)			
Vaccine efficacy			**NVX-CoV2373 N=1205**	**Placebo N=594**		

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
	First COVID-19 cases from 7 days post dose 2 in participants without prior SARS-CoV-2	n (%)	6 (0.5)	14 (2.4)	*Descriptive analysis with limited follow up and fewer observations but with similar efficacy confirmed in adults*	PP-EFF population (7 days post Dose 2), 2019-nCoV301, paediatric expansion
	Incidence rate per 100 person-years	IR (95% CI)	2.90 (1.31, 6.46)	14.20 (8.42, 23.93)		
	Vaccine Efficacy	VE % (95% CI)	**79.5 %** (46.8%, 92.1%)			
Unfavourable Effects						
Local and systemic Reactogenicity Solicited safety set			NVX-CoV2373 (N=1,487)	Saline placebo Group (N = 745)		
	Injection site tenderness	%	Dose 1: 56% Dose 2: 65%	Dose 1: 21% Dose 2: 14%	Transient events, majority mild to moderate intensity	Safety Analysis Set, 2019-nCoV301, Paediatric expansion NVX-CoV2373: N=1448/1394 (D1/D2) Placebo: N=726/686 (D1/D2)
	Injection Site Pain	%	Dose 1: 45% Dose 2: 61%	Dose 1: 17% Dose 2: 15%		
	Muscle Pain	%	Dose 1: 34% Dose 2: 49%	Dose 1: 16% Dose 2: 12%		
	Headache	%	Dose 1: 30% Dose 2: 57%	Dose 1: 25% Dose 2: 17%		
	Fatigue	%	Dose 1: 24% Dose 2: 50%	Dose 1: 15% Dose 2: 15%		
	Malaise	%	Dose 1: 15% Dose 2: 40%	Dose 1: 9% Dose 2: 7%		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The most important favourable effect of vaccination is the prevention of symptomatic disease that has been demonstrated for Nuvaxovid in the pivotal trials that were submitted for marketing authorisation. A similar degree of benefit of Nuvaxovid in adolescents 12 to <18 years of age can be inferred by the successful immunobridging approach to young adults, 18 to <26 years of age.

The predefined non-inferiority margins with respect to neutralising antibody levels and seroresponse rates were met, and GMTs of neutralising antibodies in adolescents were higher than observed in young adults following 2 doses of Nuvaxovid given 21 days apart. Therefore at least similar efficacy is expected in

adolescents as observed in young adults. Clinical data also show short-term protection against symptomatic COVID-19 in adolescents 12 to <18 years of age supporting the immunobridging approach.

The most common and important unfavourable effects are related to reactogenicity. The reactogenicity profile was found to be comparable to that observed in the adult population that was evaluated in a previous application, with the exception of fever which occurs at higher frequencies and is more often of a higher grade with decreasing age. Importantly, the overall safety profile is similar as is observed in adults and no new safety concerns were observed, however, the study size did not allow detection of rare adverse events.

3.7.2. Balance of benefits and risks

The course of COVID-19 in adolescents is generally milder than in the older population. Nonetheless, also amongst this age group, there are individuals that suffer from direct consequences of the infection. Further, considering the acceptable safety profile, which is largely characterised by mild to moderate reactions, taking into account the limited experience with this vaccine so far, it is considered that the favourable effects of preventing COVID-19 with potential irreversible and long-lasting consequences outweigh the identified risks of vaccination with Nuvaxovid.

3.8. Conclusions

The overall benefit-risk of Nuvaxovid in adolescents aged 12 to <18 years is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include use in adolescents 12 to 17 years of age for Nuvaxovid, based on data from study 2019nCoV-301, a Phase 3, Randomized, Observer-Blinded, Placebo-Controlled Study to evaluate the efficacy, safety, and immunogenicity of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine (SARS-CoV-2 rS) with Matrix-M Adjuvant in Adult Participants ≥ 18 Years with a Pediatric Expansion in Adolescents (12 to < 18 Years); as a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 1.1 of the RMP has also been submitted.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I and IIIB, and to the Risk Management Plan are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0126/2021and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'EMEA/H/C/005808/II/0009'