Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

National Procedure

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

PLGB 54180/0002

The Public Assessment Report summarises the initial assessment at the time of approval in February 2022. The text in the original report remains unchanged.

Our advice is regularly updated on the basis of significant new data and our latest advice can be found in the Summary of Product Characteristics.

Novavax CZ a.s.

LAY SUMMARY

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

This is a summary of the Public Assessment Report (PAR) for Nuvaxovid dispersion for injection. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

For practical information about using Nuvaxovid dispersion for injection, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Nuvaxovid dispersion for injection and what is it used for?
This application is a full-dossier application. This means that the results of pharmaceutical, non-clinical and clinical tests have been submitted to show that this medicine is suitable for treating the specified indications.

Nuvaxovid dispersion for injection is a vaccine used to prevent COVID-19 caused by the SARS-CoV-2 virus in adults 18 years of age and older.

How does Nuvaxovid dispersion for injection work?
Nuvaxovid dispersion for injection is a vaccine used to prevent COVID-19 caused by the SARS-CoV-2 virus and is given to adults 18 years of age and older.

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

How is Nuvaxovid dispersion for injection used?
The pharmaceutical form of this medicine is dispersion for injection and the route of administration is injection.

Nuvaxovid dispersion for injection 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).

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

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

For further information on how Nuvaxovid dispersion for injection is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should ask the administering healthcare practitioner if they have any questions concerning the medicine.

What benefits of Nuvaxovid dispersion for injection have been shown in studies?
The clinical efficacy, safety, and immunogenicity of Nuvaxovid dispersion for injection is being evaluated in two pivotal, placebo-controlled, Phase 3 studies, one conducted in North America and one in the United Kingdom, and a Phase 2a/b study conducted in South Africa.

Study 1 (2019nCoV-301)
Study 1 is an ongoing Phase 3, multicentre, randomised, observer-blinded, placebo-controlled study in participants 18 years of age and older in United States and Mexico.

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

Vaccine efficacy of Nuvaxovid dispersion for injection to prevent the onset of COVID-19 from seven days after Dose 2 was 90.4% (95% CI 82.9 – 94.6). Patients who took Nuvaxovid dispersion for injection (n=17,312) did not experience severe COVID-19 compared with 4 cases of severe COVID-19 reported in patients who took placebo (n=8,140) in the PP-EFF analysis set.

Nuvaxovid dispersion for injection showed similar efficacy in subgroup analyses for male and female participants and racial groups, and across participants with medical comorbidities associated with high risk of severe COVID-19.

The most common Variant of Concern identified during the time period of enrolment of this study was Alpha.

Study 2 (2019nCoV-302)
Study 2 is an ongoing Phase 3, multicentre, randomised, observer-blinded, placebo-controlled study in participants 18 to 84 years of age in the United Kingdom.

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

Vaccine efficacy of Nuvaxovid dispersion for injection to prevent the onset of COVID-19 from seven days after Dose 2 was 89.7% (95% CI 80.2 – 94.6). Patients who took Nuvaxovid dispersion for injection (n=7,020) did not experience severe COVID-19 compared with 4 cases of severe COVID-19 reported in patients who took placebo (n=7,019) in the PP-EFF analysis set.

Overall, 431 participants were co-vaccinated with inactivated seasonal influenza vaccines; 217 sub-study participants received Nuvaxovid dispersion for injection and 214 received placebo.
Study 3 (2019nCoV-501)

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

The PP-EFF included 2,770 participants who received either Nuvaxovid dispersion for injection (n = 1,408) or placebo (n = 1,362), received two doses (Dose 1 on day 0; Dose 2 on day 21), did not experience an exclusionary protocol deviation, and did not have evidence of SARS-CoV-2 infection through 7 days after the second dose.

A total of 147 symptomatic mild, moderate, or severe COVID-19 cases among all adult participants, seronegative (to SARS-CoV-2) at baseline, were accrued for the complete analysis of the primary efficacy endpoint.

Vaccine efficacy of Nuvaxovid dispersion for injection to prevent the onset of COVID-19 from seven days after Dose 2 was 48.6% (95% CI 28.4 –63.1). There were 51 COVID-19 cases (3.62%) in patients who took Nuvaxovid dispersion for injection (n=1,408) compared with 96 COVID-19 cases (7.05%) in patients who took placebo (n=1,362) in the PP-EFF analysis set.

The most common Variant of Concern identified during the time period of enrolment of this study was Beta.

What are the possible side effects of Nuvaxovid dispersion for injection?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on behalf of someone else they care for, directly via the Yellow Card scheme at www.mhra.gov.uk/yellowcard or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

The most common side effects with Nuvaxovid dispersion for injection (which may affect more than 1 in 10 people) are headache, feeling sick (nausea) or getting sick (vomiting), muscle ache, joint pain, tenderness or pain where the injection is given, feeling very tired (fatigue) and generally feeling unwell.

Why was Nuvaxovid dispersion for injection approved?
It was concluded that Nuvaxovid dispersion for injection has been shown to be effective in the prevention of COVID-19 caused by the SARS-CoV-2 virus in adults 18 years of age and older. Furthermore, the side effects observed with use of this product products are considered to be typical for this type of treatment. Therefore, the MHRA decided that the benefits are greater than the risks and recommended that this medicine can be approved for use.

Nuvaxovid dispersion for injection has been authorised with a Conditional Marketing Authorisation (CMA). CMAs are intended for medicinal products that address an unmet medical need, such as a lack of alternative therapy for a serious and life-threatening disease.

CMAs may be granted where comprehensive clinical data is not yet complete, but it is judged that such data will become available soon.

What measures are being taken to ensure the safe and effective use of Nuvaxovid dispersion for injection?

As for all newly authorised medicines, a Risk Management Plan (RMP) has been developed for Nuvaxovid dispersion for injection. The RMP details the important risks of Nuvaxovid dispersion for injection, how these risks can be minimised, any uncertainties about Nuvaxovid dispersion for injection (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Nuvaxovid:

Important identified risks	None
Important potential risks	• Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) • Anaphylaxis • 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

The applicant proposes the continuation of safety surveillance from 4 ongoing clinical trials:

- 2019nCoV-101; A 2-part, Phase 1/2, Randomized, Observer-Blinded Study 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
- 2019nCoV-501; A Phase 2a/b, Randomized, Observer-Blinded, Placebo-Controlled Study 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
- 2019nCoV-302; A Phase3, Randomised, Observer-Blinded, Placebo-Controlled Trial 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 United Kingdom
- 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)

The applicant proposes 5 post-authorisation safety studies including:

- 2019nCoV-402 (UK Post-Authorisation Safety Study Using the Clinical Practice Research Datalink (CPRD)
- 2019nCoV-405 (Global Pregnancy and infant outcomes study using the COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER))
- 2019nCoV-404 (US Post-authorization safety study using a claims and/or EHR (Electronic Health Record) database)
- 2019nCoV-401 (EU/EEA Post-authorisation effectiveness study based on a test-negative design using the COVIDRIVE platform)
- 2019nCoV-403 (US Post-authorization effectiveness study using a claims and/or EHR database)

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Nuvaxovid dispersion for injection are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

A RMP and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Other information about Nuvaxovid dispersion for injection
A Marketing Authorisation for Nuvaxovid dispersion for injection was granted in Great Britain (GB, consisting of England, Scotland and Wales) on 03 February 2022.

The full PAR for Nuvaxovid dispersion for injection follows this summary.

This summary was last updated in October 2022.

TABLE OF CONTENTS

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Nuvaxovid dispersion for injection COVID-19 Vaccine (recombinant, adjuvanted) (PLGB 54180/0002) could be approved.

The product is approved for the following indication:

Active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

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

Name of the active substance is COVID-19 Vaccine (recombinant, adjuvanted).

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.

This application was approved under Regulation 50 of The Human Medicines Regulation 2012, as amended (previously Article 8(3) of Directive 2001/83/EC, as amended), a full-dossier application. All clinical data submitted were from studies conducted in accordance with Good Clinical Practice (GCP).

This application was evaluated as part of the rolling review licensing route. The rolling review process is intended to streamline the development of novel medicines. As part of the process the applicant submitted increments of the dossier for pre-assessment by the MHRA, rather than submitting a consolidated full dossier at the end of the product development process.

This product has been authorised as a Conditional Marketing Authorisation (CMA). CMAs are granted in the interest of public health and are intended for medicinal products that fulfil an unmet medical need and the benefit of immediate availability outweighs the risk posed from less comprehensive data than normally required. Unmet medical needs include, for example, treatment or diagnosis of serious and life-threatening diseases where no satisfactory treatment methods are available. CMAs may be granted where comprehensive clinical data is not yet complete, but it is judged that such data will become available soon. Adequate evidence of safety and efficacy to enable the MHRA to conclude that the benefits are greater than the risks is required, and has been provided for Nuvaxovid. The CMA for Nuvaxovid, including the provision of any new information, will be reviewed every year and this report will be updated as necessary.

In line with the legal requirements for children's medicines, the application included a licensing authority decision on the agreement of a paediatric investigation plan (PIP) MHRA-100149-PIP01-21

At the time of the submission of the application the PIP was not yet completed as some measures were deferred.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Advice was sought from the Commission of Human Medicines (CHM) on 28 January 2022 as COVID-19 products are of major public interest.

A national marketing authorisation was granted in Great Britain (GB, consisting of England, Scotland and Wales) on 03 February 2022.

II QUALITY ASPECTS

II.1 Introduction

This product consists of a colourless to slightly yellow dispersion for injection presented in a multidose vial. The dispersion is clear to mildly opalescent. One vial contains 10 doses of 0.5 mL. One dose (0.5 mL) contains 5 micrograms of the SARS-CoV-2 spike protein adjuvanted with Matrix-M. Each 0.5 mL dose contains Matrix-M adjuvant consisting of: Fraction-A (42.5 micrograms) and Fraction-C (7.5 micrograms) of *Quillaja saponaria Molina* extract.

In addition to SARS-CoV-2 spike protein and Matrix-M adjuvant, this product also contains the excipients cholesterol, phosphatidylcholine (including all-rac-α-Tocopherol), potassium dihydrogen phosphate, potassium chloride, disodium hydrogen phosphate dihydrate, disodium hydrogen phosphate heptahydrate, sodium dihydrogen phosphate monohydrate, sodium chloride, polysorbate 80, sodium hydroxide (for adjustment of pH), hydrochloric acid (for adjustment of pH) and water for injections.

The finished product is packaged in a 5 mL vial (type I glass) with a stopper (bromobutyl rubber) and an aluminium overseal with blue plastic flip-off cap. Each vial contains 10 doses of 0.5 mL. Pack size: 10 multidose vials. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current Ph. Eur. quality standards.

II.2 ACTIVE SUBSTANCE

rINN: COVID-19 Vaccine (recombinant, adjuvanted)

Structure

The active substance (company code NVX-CoV2373) is the protein product of a recombinant SARS-CoV-2 S-gene encoding the 1260 amino acid spike protein (the full length 1273 amino acid protein minus the signal peptide).

The SARS-CoV-2 viral envelope consists of multimers of the spike (S) glycoprotein which mediate receptor binding and membrane fusion with the host cell. The S gene was codon optimised for expression in Spodoptera frugiperda (Sf9) insect cells from a full-length, prefusion, stabilised SARS-CoV-2 S genetic sequence. A total of five amino acid changes were introduced, including three in the S1/S2 furin cleavage site (RRAR to QQAQ) and two in the HR1 domain where 2 proline substitutions (2P) were inserted at residues K986P and V987P, respectively. It is stated that these mutations were introduced to stabilise the protein. The virus strain name is Wuhan-Hu-1 and was collected from the Wuhan seafood market in December 2019.

Purified recombinant spike (rS) glycoprotein forms trimers which bind with high affinity to the human angiotensin-converting enzyme 2 (hACE2) receptor. The 13 amino acid signal peptide is not present on SARS-CoV-2 rS and thus the rS is 1260 amino acids. The SARS CoV-2 rS protein has 22 known glycosylation sites which results in a heterogenous glycoprotein with a theoretical molecular weight of 163,997 Da.

COVID-19 Vaccine (recombinant, adjuvanted) is not the subject of a European Pharmacopoeia monograph.

Manufacture of the drug substance
The active substance is manufactured, tested and released at Serum Institute of India Pvt. Ltd. (SIIPL). The facilities involved are Serum Institute of India Pvt. Ltd. Hadapsar, Pune - 411028, Maharashtra, India and Serum Institute of India Pvt. Ltd. Manjari BK, Tal -Haveli, Pune-412307, Maharashtra, India. The SIIPL site was inspected by MHRA, UK. GMP certificates or a QP declaration have been provided for all relevant manufacturing sites, testing sites and QP release site. The manufacturer has provided details of the responsibilities of each facility involved in manufacture and testing including responsibilities performed by contract laboratories.

Description of manufacturing process and process controls
The SARS-CoV-2 rS Protein active substance is produced in a Sf9 insect cell line by using a recombinant baculovirus system. A description of the manufacturing process and controls has been provided, including material inputs, critical and non-critical process parameters, and process outputs.

The active substance manufacturing process starts with the revival, expansion and production of the Sf9 cells from the working cell bank (WCB) into shake flasks followed by bioreactor/fermenter using serum-free medium (SFM). The cells are infected by baculovirus inoculum (BVI). The spike proteins are expressed on the surface of the Sf9 cells. At the end of the growth phase, the cells are harvested by centrifugation followed by extraction using a non-ionic detergent low pH treatment, neutralisation and clarification by centrifugation (of neutralised lysate) followed by depth filtration and 0.2 μm filtration. The clarified lysate is subjected to a purification process that includes anion exchange chromatography, nanofiltration and affinity chromatography. The affinity chromatography eluate is subjected to concentration and diafiltration using tangential flow filtration (TFF) and final 0.2 μm filtration to obtain a purified SARS-CoV-2 rS protein active substance.

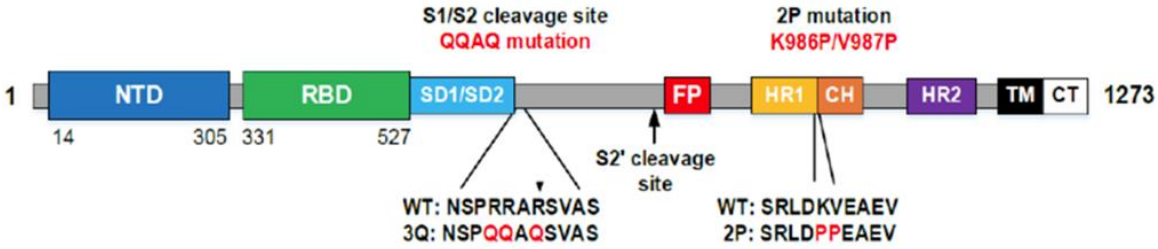
Control of materials
Raw materials
A listing of the raw materials used in the manufacturing process of the active substance is provided. All the listed raw materials are tested in compliance with their respective monographs. The release specifications of raw materials released based on the supplier certificate of analysis and/or tested with in-house developed specifications are also provided. No raw materials of animal or human origin are used during the manufacturing process of the active substance. There are three materials of biological origin used in the active substance process, namely Insect Cell Media (yeast), Nutrient feed (soy), and Affinity Resin (lentil). Appropriate quality agreements are in place between the applicant and the supplier of the proprietary media and supplements.

Baculovirus
A complete list of raw materials used for the production of the baculovirus vector is presented, including details of the step where it is used, its supplier, source and certificate of analysis. No materials of animal or human origin were used during the manufacturing process of the baculovirus vector or the master virus stock (MVS).

Information about the preparation of the recombinant baculovirus vector is provided, comprising information about the source of the genetic sequence, procedures for the generation of the vector, transfection and preparation of primary virus (P1) and pre-master virus stock (PVS, P2).

The S-protein is a trimeric glycoprotein of 1273 amino acids. The SARS-CoV-2 S glycoprotein wild type (wt) sequence was downloaded from GenBank sequence MN908947 nucleotides 21563-25384. The S gene was codon optimised for high level expression in Sf9 insect cells and biochemically synthesised by Genscript (Piscataway, NJ, USA). Three mutations (RRAR to QQAQ) were made in the S1/S2 furin site of the full-length wt SARS-CoV-2 S protein along with two additional mutations, K986P and V987P, to stabilise the protein as shown in Figure 3 and Table 1).

Figure 1: Full-length spike protein construct 3Q-2P SARS-Cov-2 rS (BV 2372)



The wild type SARS-CoV-2 S full length S gene was cloned in the pBacSV40 plasmid with a 5' polyhedron promoter and a 3' SV40 polyA sequence. The virus strain name is Wuhan-Hu-1. The sequence of the glycoprotein gene was confirmed by DNA sequencing analysis. The pBacSV40 plasmid containing wild type SARS-CoV-2 S with the QQAQ and PP sequence was confirmed by DNA sequencing. Information about the function of the individual structural elements of the plasmid is provided.

Table 1: Sequence change information from wild type for SARS-CoV-2 rS protein

Type of Modifications	Modification
Point Mutation	Lysine 986 → Proline 986 Valine 987 → Proline 987
Mutation of Cleavage Sites	Arginine 682 Arginine 683 Alanine 684 Arginine 685 → Glutamine 682 Glutamine 683 Alanine 684 Glutamine 685

The plasmid containing the SARS-CoV-2 rS gene was transfected into Sf9 cells using a cationic lipid transfection reagent to produce recombinant baculovirus BV2373. The recombinant baculovirus was plaque-purified, harvested and filtered (P0 virus stock). Detailed descriptions are given for the generation and preparation of the virus stocks. The virus banking system consists of an MVS and WVS. The testing program and results for the MVS and WVS are presented and is in accordance with the relevant Ph. Eur. monographs. Testing includes controls for mycoplasma/spiroplasma, mycobacterium, adventitious agents (NGS), virus titre, sterility and nucleotide sequence analysis.

Cell bank

Sufficient information is provided about the source history and generation of the Sf9 cell substrate. Sf9 cell banks contain cells from the fall armyworm, Spodoptera frugiperda (Lepidoptera; butterflies and moths). Sf9 cells were derived from cells purchased from the American Type Culture Collection (ATCC) that were adapted to grow in suspension culture in serum-free medium. The preparation of the pre-master cell bank, master cell bank (MCB), working cell bank (WCB) and end-of-production cell bank (EOPCB), is described. Testing of the cell banks is in line with ICH Q5A (R1) and ICH Q5D. The cell banks were tested for identity, safety, and purity, and all test results met the acceptance criteria. Testing of cell banks includes controls for sterility, mycoplasma, mycobacterium, spiroplasma, endotoxin, in

vitro adventitious agents, in vivo adventitious agents, in vitro assay for bovine virus, karyotype, isoenzyme, Type C particles, retrovirus (reverse transcriptase activity), co-cultivation, product enhanced reverse transcriptase, cell growth, virus replication, PCR assay for detection of specific porcine and bovine viruses. All cell banks have tested negative for viruses, with the exception of the Sf9 Rhabdovirus which is known to be present in Sf9 cells.

Controls of critical steps and intermediates
Critical process parameters (CPPs), in-process controls (IPCs) and critical quality attributes (CQAs) are defined. Appropriate in-process controls and intermediate specifications are applied. The controls (in-process bioburden and endotoxin measurements) used to demonstrate microbial control of the manufacturing process for drug substance are described and found acceptable.

Process validation and/or evaluation
Process characterisation of active substance was performed in parallel with the PPQ campaign at SIIPL as part of a non-traditional approach to enable rapid deployment of a manufacturing process of commercial production, in response to the current global pandemic. The process validation campaign was performed with the equipment intended for the commercial active substance manufacturing process. Additional supportive studies were performed prior to or concurrent to the PPQ campaign to support process validation. These comprised studies on stability of the Sf9 End of Production Cells, WVS hold time studies, buffer biochemical stability studies, process intermediate biochemical stability studies, resin lifetime and re-use studies, residual impurities (including for process-related impurities and residual DNA), viral clearance studies, extractables and leachable risk assessments and filter validation studies. Summaries of these studies are provided. Collectively, the PPQ data overall provides scientific evidence that each stage of the active substance manufacturing process, when executed according to the production batch records, consistently produces an active substance that meets its product specification. However, to further address the assurance of the impurity profile, the applicant has committed to explore possibilities to further optimise the manufacturing process with regard to removal of impurities.

Manufacturing process development
A summary of Novavax's manufacturing lots used in clinical studies is provided. Lots were manufactured in the US at Emergent BioSolutions, Inc (EBSI) and Fujifilm Diosynth Biotechnologies (FDBU). Lots manufactured and their respective use to date are described. Multiple changes were introduced during active substance process development. Several changes have been introduced which increased product purity. Extensive comparability testing results were provided and discussed in detail. In view of the complexity of the active substance, some variability between batches produced at the different sites may be expected. It is noted that some of the differences are indeed intended (increased purity, different protein and PS80 content). The SIIPL commercial process lots are not considered fully comparable from a quality perspective for potency and binding kinetics when compared with the EBSI/FDBU materials used in the clinical studies. SIIPL active substance batches have higher purity when compared to active substance batches used in preparation of finished product batches applied in phase 2 and phase 3 clinical studies and hence comparability is not demonstrated for this quality attribute. However, these differences can be justified as they are not expected to have an adverse impact on safety or efficacy profiles. This is further supported by the results from clinical study 2019nCoV-101 (two-part phase 1/2 randomised observer blinded study designed to evaluate the safety and immunogenicity of NVX-CoV2373). Although higher frequencies of local and systemic reactogenicity occurred in participants receiving the higher antigen dose (25 μg) compared to the lower antigen dose (5

µg), the safety profile was overall considered acceptable. The proposed upper limit for protein content is significantly lower than the 25 µg/0.5 mL dose used in the phase 1/2 studies. The particle size distribution ranges overall are comparable.

Characterisation
Structural characteristics of the rS protein and particle characteristics have been investigated using a variety of orthogonal methods. The active substance particles consist of rS trimers and PS80 micelles that form a complex. The ACE2-receptor binding domain (RBD) of the spike protein faces outward from a core of PS80 molecules with the rS C-terminal hydrophobic transmembrane region facing toward the micelle interior. This arrangement of multiple rS trimers around a PS80 core is referred to as a rosette. Inter-trimer interactions between rS proteins were also observed resulting in higher order spike multimers. Product-related and process-related impurities have been identified and characterised. Some residual host cell (Sf9) and baculovirus proteins were found to be present in the clinical and commercial batches. Overall, sufficient information on the characterisation of the molecule has been provided. A number of post-authorisation commitments have been agreed with the applicant (recommendations) to provide data to further substantiate this conclusion. Considering the purity levels of the batches used in clinical studies, and the purity levels of commercial process batches, the specification for purity of rS content is acceptable for the conditional marketing authorisation.

Control of drug substance
The active substance specifications include general tests (appearance, pH, PS-80), protein concentration, identity , purity, potency, residual DNA and safety tests (endotoxin, bioburden, mycoplasma/spiroplasma, harvest contamination). The manufacturer has provided adequate justification for these limits, based on efficacy and safety considerations.

Validation of analytical procedure
Validation of the analytical methods used for the control of the drug substance are satisfactory for ensuring compliance with the relevant specifications.

Batch analyses
Batch release results for all batches used in the clinical trials, along with site of manufacture, have been provided and show that all batches conformed to the specifications in force at time of manufacture. Batch analysis data of active substance batches manufactured as SIIPL have been provided. The results are within specifications and confirm consistency of the manufacturing process.

Reference standard
The Reference Standard which is currently used for the potency assay is an intermediate reference standard. This standard was prepared from representative active substance and was calibrated against active substance used in the Phase 3 clinical studies. This provides a link between the reference standard and clinical study material. A protocol has been provided for the calibration of the new primary and working reference standard. After calibration, the new primary reference standard will be bridged against the intermediate reference standard and previous Reference Standard.

Container closure system
The choice of container/closure is adequately described and justified. Stability testing has shown the primary container to be compatible with the drug substance. The primary packaging has been shown to comply with the quality standards of the Ph. Eur.

Stability
The stability data provided are sufficient to support the proposed shelf-life of 9 months for the drug substance stored at <-60°C. The company has committed to continue the stability studies

II.3 DRUG PRODUCT

Pharmaceutical development
A satisfactory account of the pharmaceutical development has been provided. All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients. The finished product composition is described in Table 2 below:

Table 2: Finished product composition

Name of Ingredient	Function
SARS-CoV-2-rS	Immunogen / Active ingredient
Disodium hydrogen phosphate heptahydrate[4]	Formulation Buffer Agent
Sodium dihydrogen phosphate monohydrate	Formulation Buffer Agent
Sodium chloride	Formulation Buffer Agent – Isotonicity adjuster
Polysorbate 80	Formulation Buffer Agent - Stabilizer
Sodium hydroxide	pH Adjustment
Hydrochloric acid	pH Adjustment
Water for Injections	Vehicle
Matrix-M Adjuvant[2]	
Fraction-A	Adjuvant
Fraction-C	Adjuvant
Cholesterol	Formulation Agent
Phosphatidylcholine[3]	Formulation Agent
Potassium dihydrogen phosphate	Buffer
Potassium chloride	Tonicity Agent
Disodium hydrogen phosphate dihydrate	Formulation Buffer Agent
Sodium chloride	Formulation Buffer Agent
Water for Injections	Vehicle

[1] Nominal Concentration.

The finished product is formulated on the basis of the total protein concentration of the active substance and a 5% overage is used to compensate for any potential loss during finished product manufacturing.
The vials are filled with a minimum of 6.0 mL to ensure that 10 doses of 0.5 mL can be withdrawn.

Novel excipient – adjuvant
The Matrix-A and Matrix-C adjuvant components contain purified, chromatographic fractions (A and C) of enriched purified bark extract from the tree *Quillaja saponaria* Molina (saponins) as well as cholesterol from botanical origin, and phosphatidylcholine, from hen's egg yolk. Matrix-A and Matrix-C are regularly shaped, uniform and stable complexes (nanoparticles) suspended in phosphate buffered saline (PBS). Cholesterol and phosphatidylcholine are present as excipients in the Matrix formulation. Characterisation has been conducted with several orthogonal methods for chromatographic profile, identity, monosaccharide analysis, haemolytic activity, particle size and structure. The impurities related to the manufacture of Matrix-A and C have been adequately discussed. The control specification comprises tests for appearance, identification, concentrations of saponin (SA),

cholesterol (CH) and phosphatidylcholine (PC), saponin purity, residual detergent N-Decanoyl-N-methylglucamine, pH, average particle size, ratio CH/SA, ratio PC/SA, bioburden and endotoxins. The specifications and shelf-life will be further reviewed post-approval based on updated characterisation and stability data.

Based on batch release results, results of characterisation tests and the preliminary results of the comparative accelerated stability studies, it is concluded that clinical finished product batches are sufficiently comparable to commercial finished product produced at SIIPL.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product
A description and flow-chart of the manufacturing method has been provided.

The manufacturing process is described in sufficient detail, including the equipment and materials used, formulation calculations, critical and non-critical process parameters with operating ranges/set points and in-process controls. The process principally involves the preparation of the formulation buffer and active substance, preparation of Matrix-M adjuvant by mixing Matrix-A and Matrix-C, preparation of the co-formulated final bulk, sterile filtration of the co-formulated bulk to the filling machine (isolator), filling into sterilised vials and finishing. All critical steps are adequately controlled. A number of in-process controls are proposed for the manufacturing process and these are considered satisfactory. The PPQ studies confirm that the commercial process performs effectively and is able to produce a finished product meeting its predetermined controls and acceptance criteria.

Finished product specification
The finished product specifications include general tests (appearance, pH, osmolality), protein concentration, identity , potency, content of Matrix-A and -C, safety tests (endotoxin, bioburden), extractable volume and container closure integrity (CCIT). The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications.

Independent batch testing
Independent batch testing is required for vaccines and provides additional assurance of quality before a batch is made available to the market. Independent batch testing is a function that is undertaken by an Official Medicines Control Laboratory (OMCL). The UKs National Institute for Biological Standards and Control (NIBSC) is responsible for this function. Independent batch testing is product-specific and highly technical: it requires specific materials and documentation from the manufacturer and comprises laboratory-based testing and review of the manufacturer’s test data. If all tests meet the product specifications a certificate of compliance is issued by the OMCL.

Characterisation of impurities
There are no new process related drug product impurities in addition to those described for the drug substance.

Container closure system
The container closure system has been well described and complies with the relevant quality standards of the Ph. Eur.

Stability
Finished product stability studies include batches of the finished product stored in the packaging proposed for marketing. A shelf-life of 9 months at 2-8 °C is accepted based on the supporting data. However, the applicant is required to provide monthly updates for the PPQ lots manufactured at SIIPL using the specified manufacturing process and three PPQ lots manufactured at SIIPL using the commercial scale manufacturing process. This data is required to achieve a comprehensive data package and ensure consistent product quality during shelf-life and is therefore requested as a Specific Obligation.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

Based on the stability information currently available, a shelf-life of 9 months can be accepted, with the following storage conditions:
Store in a refrigerator (2°C to 8°C).
Do not freeze.
Keep the vials in the outer carton in order to protect from light.

Shelf-life
Unopened vial
9 months at 2°C to 8°C, protected from light.
Unopened Nuvaxovid vaccine has been shown to be stable up to 12 hours at 25°C. Storage at 25°C is not the recommended storage or shipping condition but may guide decisions for use in case of temporary temperature excursions during the 9-month storage at 2°C to 8°C.

Punctured vial
Chemical and physical in-use stability has been demonstrated for 6 hours at 2°C to 25°C from the time of first needle puncture to administration.
From a microbiological point of view, after first opening (first needle puncture), the vaccine should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The MHRA considered that the quality data submitted for this application are satisfactory.

The grant of a marketing authorisation is recommended.

The CHM considered that the quality data submitted in support of this application are sufficient to support a CMA, taking into consideration the pandemic context. The CHM noted the specific obligations and recommendations imposed on the EU authorised product. They recommended that the GB licence imposes the same conditions to support alignment with the product information for Northern Ireland. CHM has also made further recommendations regarding quality, to be implemented post-approval. A summary of these is below. The list of recommendations as proposed by the CHMP are detailed in the CHMP Public Assessment Report.

The CHM's recommendations to be implemented post-authorisation include:

- to further optimise the manufacturing process regarding removal of impurities
- to further characterise the starting materials used to manufacture the active substance
- to update ongoing process validation reports

- to further characterise the active substance, adjuvant and finished product
- to develop assays to better control host cell and baculovirus impurities in the active substance
- to implement additional assays to better control finished product consistency
- to review finished product specifications once sufficient commercial batch data are available
- to update stability data for the active substance, adjuvant and starting materials
- to provide stability data for the raw materials and reference standards used in the manufacture of the adjuvant, and to tighten the specifications for the adjuvant.

Details on specific obligations are given in Section VI.

III NON-CLINICAL ASPECTS

III.1 Introduction

The following non-clinical studies were submitted with this application:

Table 3: Summary of nonclinical pharmacology studies evaluating SARS-CoV-2 rS with Matrix-M adjuvant*

* (also described as Matrix-M1 in study documents)

Study	Animals (n)	Study design (treatment groups/ administration/endpoints)	Key conclusion
Immunogenicity of various SARS-CoV-2 vaccine candidates (complete)	BALB/c mice (n = 4-8/group)	1 and 10 µg SARS-CoV-2 3Q BV2365 ± 5 µg Matrix-M1 1 and 10 µg SARS-CoV-2 3Q-ΔFP806-815 BV2369 ± 5 µg Matrix-M1 1 and 10 µg Scripps RBD ± 5 µg Matrix-M1 Placebo Administered IM on Days 0 and 14 Immunogenicity evaluations (anti-S IgG and hACE2 binding inhibition) on Days -1 (pre-dose), 13, 21, and 28	The full-length S protein construct bearing the 3Q substitution (BV2365) was modestly immunogenic in the absence of adjuvant but was highly immunogenic with the addition of Matrix-M1 adjuvant and induced functional antibodies. • The BV2369 construct with the 3Q-ΔFP806-815 substitutions and deletions in the hydrophobic fusion peptide was immunogenic by the anti-S IgG measure; however, hACE2 binding inhibiting functional antibodies were not detected. • For the RBD construct, anti-S IgG and hACE2 binding inhibiting titres were at the assay limit of detection for the 1 µg dose and very low levels were detected on Day 28 at the 10 µg dose.
Cellular and humoral immune responses (complete)	BALB/c mice (n = 3-6/group)	10 µg SARS-CoV-2 rS ± 5 µg Matrix-M1 Placebo Administered IM on Days 0 and 21 Immunogenicity evaluations (anti-S IgG, hACE2 binding inhibition) on Days -1 (pre-dose), 20, and 28 CMI evaluations to assess Th1/Th2 response (ELISpot, flow cytometry) on Day 28 (spleen)	High titre, functional immune responses (i.e, anti-S IgG antibodies, hACE2 binding inhibiting antibodies, and antigen-specific T-cell responses) were observed; the addition of Matrix-M1 adjuvant provided higher immune responses compared with antigen alone. • SARS-CoV-2 rS induced high levels of Th1-type CD4+ T-cell responses to SARS-CoV-2 rS protein, which included polyfunctional effector phenotypes. • Matrix-M1 adjuvant-associated enhancement of splenic Tfh and GC B-cell populations suggests favourable conditions for establishment of a diverse, high-affinity, and durable antibody response.

Cellular and humoral immune responses (complete)	BALB/c mice (n = 10/group)	1 or 10 µg SARS-CoV-2 rS unadjuvanted 1 or 10 µg SARS-CoV-2 rS + 5 µg Matrix-M1 1 or 10 µg SARS-CoV-2 rS + 200 µg aluminum hydroxide Administered IM on Days 0 and 21 Immunogenicity evaluations (hACE2 binding inhibition) on Days 20 and 35 CMI and Th1/Th2 evaluations: ELISA for IgG1/2a on Days 20 and 35 (serum); cytokine fluorospot on Day 35 (spleen and draining lymph nodes)	Immune response induced by Matrix-M1-adjuvanted SARS-CoV-2 rS vaccine was balanced in its Th1/Th2 cellular immune response, with a supportive IgG1/IgG2a ratio; whereas Alum-adjuvanted SARS-CoV-2 rS vaccine primarily induced a Th2-skewed humoral and cellular immune response.
Cellular and humoral immune responses (ongoing; data through 6 months provided)	Olive baboons (n = 2-3/group)	25 µg SARS-CoV-2 rS unadjuvanted 1, 5, or 25 µg SARS-CoV-2 rS + 50 µg Matrix-M1 Administered IM on Days 0 and 21 Immunogenicity evaluations (anti-S IgG, hACE2 binding inhibition, neutralization) on Days 0 (pre-dose), 21, 28, 35, 49, 120, and 182 CMI evaluations to assess Th1/Th2 response (flow cytometry, ELISpot) using PBMCs on Days 28, 49, and 182	SARS-CoV-2 rS with Matrix-M1 adjuvant was strongly immunogenic in baboons, most notably at the 5 and 25 µg doses. Matrix-M1 adjuvant provided antigen-sparing and enabled the induction of strong functional antibody responses compared with the unadjuvanted group. • Strong antigen-specific, Th1-skewed CD4+ Tcell responses were observed in all animals immunized with SARS-CoV-2 rS in the presence of Matrix-M1 adjuvant. • Long-term evaluation of the immune responses showed that SARS-CoV-2 rS specific antibody and cell-mediated responses were measurable in baboons for at least six months post vaccination. Notably, Th1 (IFN-γ) cytokine producing cells were detected indicating the maintenance of antigen-specific T-cell population.
Immunogenicity and protective efficacy challenge study to evaluate SARS-CoV-2 vaccine candidates (complete)	Balb/c mice (n = 4-8/group)	1 and 10 µg SARS-CoV-2 3Q BV2365 ± 5 µg Matrix-M1 1 and 10 µg SARS-CoV-2 3Q-ΔFP806-815 BV2369 ± 5 µg Matrix-M1 1 and 10 µg SARS-CoV-2 rS (BV2373) ± 5 µg Matrix-M1 Placebo Administered IM on Days 0 and 14 Immunogenicity evaluations (anti-S IgG, hACE2 binding inhibition, neutralization) on Days -1 (pre-dose), 13, 21, 28, and 42 Challenge (selected groups) on Day 69 with necropsy on Day 73	Immunization with all three constructs resulted in anti-S IgG titres that were enhanced by the addition of Matrix-M1 adjuvant; however, only BV2365 and BV2373 elicited functional antibodies. • Administration with 10 µg of unadjuvanted BV2365 or BV2373 resulted in reduced lung viral load after SARS-CoV-2 live virus challenge, while the addition of Matrix-M1 adjuvant resulted in undetectable viral levels in lungs after challenge. • This study demonstrated that the BV2365 (3Q) and BV2373 (3Q-2P) constructs were similarly immunogenic and protective in mice, supporting the continued development of the more stable 3Q-2P BV2373 construct.
Immunogenicity and protective efficacy challenge study to evaluate SARS CoV-2 rS (complete)	Balb/c mice (n = 10/group)	10 µg SARS-CoV-2 rS unadjuvanted 0.01, 0.1, 1, and 10 µg SARS-CoV-2 rS + 5 µg Matrix-M1 Placebo Administered IM on Day 0 and 14 (or Day 14 only) Immunogenicity evaluations (anti-S IgG, hACE2 binding inhibition, neutralization) on Days -1 (pre-dose), 13, 21, and 28 Challenge on Day 56 with necropsy (histopathology) on Days 60 or 63	SARS-CoV-2 rS adjuvanted with Matrix-M1 elicited high levels of anti-S IgG titres and functional antibodies, which were significantly enhanced by Matrix-M1 adjuvant and dependent on antigen dose and regimen; doses of 1 and 10 µg SARS-CoV-2 with Matrix-M1 adjuvant administered in the two-dose regimen induced the best immune responses. • SARS-CoV-2 rS with Matrix-M1 adjuvant provided protection against SARS-CoV-2 challenge in a dose-

			dependent manner as evidenced by reduction in weight loss and viral titres. • Low, suboptimal doses of SARS-CoV-2 rS vaccine did not show evidence of vaccine enhanced disease in challenged mice.
Immunogenicity and protective efficacy challenge study to evaluate SARS-CoV-2 rS (complete)	Golden Syrian hamster (n = 8/group)	1 and 10 µg SARS-CoV-2 rS + 15 µg Matrix-M1 Placebo Administered IM on Days 0 and 14 (or Day 0 only) Immunogenicity evaluations (anti-S IgG, hACE2 binding inhibition, neutralizing) on Days -1 (pre-dose), 14, 21, and 29 Challenge on Day 35 with necropsy (histopathology) on Days 39 or 49/50	• Immunization with one dose of 10 µg SARS-CoV- 2 rS with 15 µg Matrix-M1 or two doses of 1 µg or 10 µg SARS-CoV-2 rS with 15 µg Matrix-M1 resulted in robust immune responses that were enhanced with the higher antigen dose and with a second vaccination. • All SARS-CoV-2 rS vaccination doses and regimens evaluated resulted in protection from body weight loss, changes in activity level, viral replication, and lung pathology after SARS-CoV- 2 live virus challenge compared with placebo; there was no evidence of vaccine-enhanced disease following exposure to SARS-CoV-2.
Immunogenicity and protective efficacy challenge study to evaluate SARS-CoV-2 rS (complete)	Cynomolgus macaque (n = 4/group)	2.5 µg SARS-CoV-2 rS + 25 µg Matrix-M1 5 µg SARS-CoV-2 rS + 25 or 50 µg Matrix-M1 25 µg SARS-CoV-2 rS + 50 µg Matrix-M1 Placebo Administered IM on Days 0 and 21 (or Day 0 only) Immunogenicity evaluations (anti-S IgG, hACE2 binding inhibition, neutralizing) on Days 0 (pre-dose), 21, and 33 Challenge on Day 35 with necropsy (histopathology) on Day 42	Strong anti-S IgG titres, as well as functional antibody responses, were observed across all dose levels. The responses observed with the human dose of 5 µg SARS-CoV-2 rS adjuvanted with 50 µg Matrix-M1 were comparable to those observed with the higher antigen dose level (25 µg). The 2.5 µg SARS-CoV-2 rS adjuvanted with 25 µg Matrix-M1 yielded strong antibody and functional immune responses that were approximately 2- to 3-fold lower when compared to full human doses. • All vaccinated animals, including those administered with low antigen/adjuvant doses and single-dose regimens, were protected against SARS-CoV-2 live virus as evidenced by the absence of sgRNA, an assay that measures newly replicating virus, in BAL and nasal swabs. • SARS-CoV-2 rS was well tolerated and safe from any obvious vaccine-induced disease exacerbation response following exposure to SARS-CoV-2.
Immunogenicity and protective efficacy challenge study to evaluate SARS CoV-2 rS (complete)	Rhesus macaque (n = 2 5/group)	5 µg SARS-CoV-2 rS + 50 µg Matrix-M1 25 µg SARS-CoV-2 rS + 50 µg Matrix-M1 Placebo Administered IM on Days 0 and 21 (or Day 0 only) Immunogenicity evaluations (anti-S IgG, hACE2 binding inhibition, neutralizing) on Days 0 (pre-dose), 21, and 31/32 Challenge on Day 38 with necropsy (histopathology) on Day 45/46	Immunization with one dose of 5 or 25 µg SARSCoV- 2 rS with 50 µg Matrix-M1 adjuvant resulted in robust antibody responses that increased with a second vaccination; comparable immune responses were generated across the antigen dose range evaluated. • Compared with placebo, immunization with one dose of SARS-CoV-2 rS resulted in partial protection against viral replication in upper and lower airways, and immunization with two doses of SARS-CoV-2 rS resulted in near total protection against viral replication in upper and lower airways. • Clinical observations, radiographic analysis, and histopathological

			analysis did not identify clear differences between immunized and placebo animals; no evidence of vaccine-enhanced disease was observed.
Long-term immunogenicity and protective efficacy (ongoing; data through Day 57 provided)	Rhesus macaque (n = 6/group)	5 µg SARS-CoV-2 rS + 50 µg Matrix-M1 Administered IM on Days 0 and 28 Immunogenicity evaluations (anti-S and anti-RBD IgG) on Days -7, 14, 28, 32, 42, and 57 CMI and Th1/Th2 evaluations: immunophenotyping and ICCS by flow cytometry; ELISpot *Additional samples to be collected for evaluation through Day 365 with challenge planned on Day 365*	Immunization elicited high levels of S-specific and RBD-specific antibodies and immune cells that were further increased by the second immunization. • Changes in circulating immune cell abundance post-vaccination were consistent with typical responses to a potent adjuvant, as well as recruitment of lymphocytes to lymphoid organs. • B-cell responses post-boost were consistent with a rapid recall of memory B cells. • T-cell responses indicated a Th1-skewed response, and the presence of circulating Tfh cells after the boost suggested ongoing germinal centre reaction.

Abbreviations: anti-S IgG, anti-spike immunoglobulin G; BAL, bronchoalveolar lavages; CMI, cell-mediated immune(ity); ELISA, enzyme-linked immunosorbent assay; ELISpot, enzyme linked immunosorbent spot; EPL, Experimental Pathology Laboratories, Inc. (Sterling, Virginia, US); GC, germinal centre; GLP, Good Laboratory Practice; hACE2, human angiotensin converting enzyme 2; ICCS, intracellular cytokine staining; IFN-γ, interferon gamma; IM, intramuscular(ly); N, number; NLS, Noble Life Sciences; OUHSC, Oklahoma University Health Sciences Centre; PBMCs, peripheral blood mononuclear cells; RBD, receptor binding domain of the spike protein; SARS-CoV-2 3Q BV2365, "3Q" construct full-length S protein with furin cleavage site substitutions; SARS-CoV-2 3Q-ΔFP806-815 BV2369, S protein construct with deletions in the hydrophobic fusion peptide; SARS-CoV-2 rS, severe acute respiratory syndrome coronavirus 2 recombinant spike protein (clinical candidate vaccine), a "3Q-2P" construct with furin cleavage site and 2 proline substitutions (BV2373); sgRNA, subgenomic RNA; SVA, Swedish Veterinary Institute; Tfh, T follicular helper; Th1, T helper 1; Th2, T helper 2; UMSOM, University of Maryland School of Medicine (Baltimore, Maryland, US).

Table 4: Summary of nonclinical toxicology studies evaluating SARS-CoV-2 rS with Matrix-M adjuvant

Study	Animals (n)	Study design (treatment groups/ administration/endpoints)	Key conclusion
Repeat-dose toxicity			
57-day repeat-dose GLP toxicity study of SARS-CoV-2 rS with Matrix-M1 adjuvant (complete)	NZW rabbits (n = 30/group)	Placebo 50 µg SARS-CoV-2 rS [no adjuvant] 50 µg SARS-CoV-2 rS + 50 µg Matrix-M1 Administered IM on Days 1, 8, 15, and 36 Necropsies: Day 18 (interim, 5/sex/group); Day 39 (main, 5/sex/group); Day 57 (recovery, all surviving) Immunogenicity evaluations (anti-S IgG) on Days 0 (pre-dose), 7, 14, 35, and 57	SARS-CoV-2 rS with or without Matrix-M1 adjuvant was well tolerated with no effect on mortality, cageside observations, physical examination findings, Draize scores of the injection sites, body weights, food consumption, body temperatures, ocular examination findings, absolute and relative organ weights, or macroscopic observations at necropsy. • Effects on clinical pathology parameters (fibrinogen, CRP, and/or globulin), which resolved during the recovery interval, and histopathology (subacute inflammation at injection sites and adjacent tissue), which were decreased at the recovery interval, were consistent with immune stimulation following administration of a vaccine. • Anti-S IgG results confirmed vaccine delivery and demonstrated 100% seroconversion.
Genotoxicity			
Non-GLP bacterial reverse mutation assay (complete)	Not applicable	Vehicle (PBS), 0.3 to 1000 µg/plate Matrix-M1, or positive control using *S. typhimurium* strain histidine mutations and *E. coli* strain tryptophan mutation ± S9 rat liver homogenate	Matrix-M1 adjuvant at concentrations up to 1000 µg per plate was negative (non-mutagenic).

Non-GLP mammalian chromosome aberration assay (complete)	Not applicable	Vehicle (PBS), 0.68 to 100 µg/mL Matrix-M1, or positive control in CHO cells ± S9 rat liver homogenate	Matrix-M1 adjuvant at concentrations up to 100 µg/mL was negative with no significant increases observed for the induction of micronuclei.
GLP bacterial reverse mutation assay (complete)	Not applicable	Vehicle (PBS), 50 to 4400 µg/plate Matrix-M1, or positive control using *S. typhimurium* strain histidine mutations and *E. coli* strain tryptophan mutation ± S9 rat liver homogenate	Matrix-M1 adjuvant at concentrations up to 4400 µg per plate was non-mutagenic for all tester strains in the presence or absence of S9 rat liver (excepting strain TA98 in the absence of S9 activation, which was only tested up to 1000 µg per plate Matrix-M1 adjuvant due to contamination and limited amount of test article).
GLP mammalian cell micronucleus assay (complete)	Not applicable	Vehicle (PBS), 12.5 to 440 µg/mL Matrix-M1, or positive control in CHO cells ± S9 rat liver homogenate	Matrix-M1 adjuvant at concentrations up to 440 µg/mL was negative for induction of micronuclei in both non-activated and S9-activated test systems.
Reproductive toxicity			
Immune response (complete)	Sprague Dawley rat (n=4/sex/group)	10 µg SARS-CoV-2 rS + 20 µg Matrix-M1 Administered IM on Days 1 and 15 Immunogenicity evaluations (anti-S IgG) on Days -1, 14, 22, and 29	Both female and male rats generated strong anti-S IgG titres supporting the initiation of the GLP developmental and reproductive toxicology study in this animal model.
GLP developmental and reproductive toxicity study of SARS-CoV-2 rS with Matrix-M1 Adjuvant or Matrix-M1 alone (complete)	Sprague Dawley rat (n = 50/group)	Placebo 10 µg Matrix-M1 5 µg SARS-CoV-2 rS + 10 µg Matrix-M1 Administered IM on Day 1 (27 days before cohabitation), Day 15 (13 days before cohabitation), GD 7, and GD 15 Necropsies: Caesarian section GD 21 (n = 25/group); Natural delivery (n = 25/group) on PND 21 Immunogenicity evaluations (anti-S IgG) on Days -3 15, 28, GD 21, and PND 21 (dams) or GD 21 and PND 21 (offspring)	Administration of SARS-CoV-2 rS with Matrix-M1 adjuvant or Matrix-M1 adjuvant alone had no effect on mortality, physical examinations, cageside observations, body weights, body weight changes, estrus cyclicity, or food consumption during the precohabitation, gestation, or developmental periods in dams. • In the uterine cohort, there was no difference between fetal body weights, survival, or external, visceral, or skeletal exams. • In the developmental cohort, there were no differences in number of male and female pups, pup body weights, survival, litter size and sex, developmental markers, or gross pathology findings. • SARS-CoV-2 rS with Matrix-M1 adjuvant elicited robust anti-S IgG titres with a 100% seroconversion rate. Maternal anti-S IgG antibodies were detected in both fetal and pup samples confirming transfer of antibodies during gestational and postnatal stages of development; albeit pups exhibited significantly higher levels of maternal antibodies than fetuses.

Abbreviations: anti-S IgG, anti-spike immunoglobulin G; CHO, Chinese Hamster Ovary; CRP, C-reactive protein; GD, Gestational Day; GLP, Good Laboratory Practice; IM, intramuscular(ly); NZW, New Zealand White (rabbits); PBS, phosphate-buffered saline; PND, Postnatal Day; SARS-CoV-2 rS; severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine.

III.2 Pharmacology

Data on immunogenicity and protection from challenge with SARS CoV-2 virus was presented from studies in mice, in hamsters and in monkeys. These studies were performed in order to characterise the humoral and cellular responses to vaccination and to also demonstrate the additional effect of the adjuvant, Matrix M1.

In these species, vaccination resulted in IgG responses to the spike protein of SARS CoV-2 virus which resulted in blockade of engagement of virus with human ACE2. These IgG responses were boosted by the adjuvant. The adjuvant has been shown to be necessary for optimal immunogenicity and its mode of action has been demonstrated to a sufficient degree.

CD4+ T cell responses were biased towards a Th1 response, eliciting IFN-γ and IL-2 compared to IL-4. Circulating Tfh cells were also observed after boosting, suggesting ongoing germinal centre reactions.

Vaccination protected all species from adverse effects in the respiratory system after SARS CoV-2 challenge. One dose of unadjuvanted vaccine had limited immunogenicity, two doses, 21 days apart, was notably more immunogenic, with additional immunogenicity demonstrated with addition of the adjuvant. The principle that two doses of adjuvanted vaccine given some time apart was established by these data.

After vaccination, there was no indication that SARS-CoV-2 live virus challenge resulted in worsening of the inflammatory response, or of a worse in-life course of disease (e.g. body weight, general activity). Similarly, viral loads in lungs and lung histopathology were all indicative of only a reduction in disease. Cellular immune responses induced by SARS CoV-2 rS with Matrix-M1 adjuvant were generally Th1-dominant. Thus, no risk of vaccine-associated enhanced respiratory disease was seen across all these studies.

To summarise, vaccination produced antibodies to the SARS-CoV-2 S protein which act to block the engagement of the virus with ACE2 so preventing infection of cells, resulting in reduced viral loads with reduced pathology, on encountering the virus. Sufficient data was presented to support clinical use of the vaccine with its adjuvant.

III.3 Pharmacokinetics

No new pharmacokinetic data were provided and none were required for this application.

III.4 Toxicology

The general toxicities were studied in compliance with Good Laboratory Practice in rabbits given the intended human dose. Rabbits were dosed with SARS-CoV-2 rS on 4 occasions which is ample to support an initial clinical posology of two doses of the vaccine (5 µg per dose in humans) with Matrix-M1 adjuvant (50 µg per dose), 21 days apart. The same route, intramuscular, as is intended in humans was used in rabbits. Male and female animals were used. SARS-CoV-2 rS vaccine with or without Matrix-M1 adjuvant was shown to be immunogenic in all rabbits tested, supporting this choice of species for toxicological evaluation.

In the toxicity study, there were transient acute phase reactions, but no toxicity was identified that would be a concern for human use. There were local immunoinflammatory reactions at injection sites. There were also findings of reversible enlargement of the lymph nodes draining the injection sites which are attributed to an expected response to a vaccine and not to reflect toxicity. Rabbits tolerated a dose of 50 µg of antigen, compared to a proposed clinical dose of 5 µg. The adjuvant dose is the same between rabbit and human (50 µg); other toxicity studies used double this dose without eliciting notable toxicity. These data are sufficient to support a conclusion that the vaccine does not affect male fertility in rabbits: no effects indicating such were seen in the reproductive organs. Local tolerance was assessed in the general toxicity studies and separate evaluations are not needed.

Genotoxicity studies were not done with the vaccine: these were done with the Matrix-1 M1 adjuvant. No specific concerns was identified in studies in compliance with GLP. Carcinogenicity studies are not needed given the short exposure to the product.

Data from a developmental and reproductive toxicity study in compliance with GLP in pregnant rats has shown no adverse findings. Rats were confirmed as showing an immune response to SARS-CoV-2 rS adjuvanted with Matrix-M1.

The vaccine in intended for use in adults aged 18 and over. No juvenile animal studies are needed, including as there is no cause for such based on the general toxicity studies presented.

In summary, the vaccine induced local injection site reactions with transient systemic inflammation, all considered well tolerated and transient. The conclusion to date is that the data are adequate to support the clinical use of this vaccine.

III.5 Ecotoxicity/Environmental Risk Assessment

In accordance with the CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447100), due to their nature vaccines and lipids are unlikely to result in a significant risk to the environment. Therefore, environmental risk assessment studies are not provided in this application for Marketing Authorisation, which is considered acceptable.

III.6 Discussion on the non-clinical aspects

These data support the claim that the vaccine is active to protect against exposure to SARS CoV-2 virus and there is no safety concern identified concerning human use, based on the toxicity studies presented. The grant of a marketing authorisation is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

The immunogenicity, efficacy and safety data supporting this application have been generated by four studies, presented below. Nuvaxovid dispersion for injection is referred to as Nuvaxovid or NVX-CoV2373 in this clinical review.

Table 5: Overview of clinical studies

Study ID	No. of study centres/ locations	Design	Study Posology	Study Objective	Subjs by arm planned (treated)	Gender M/F Median Age	Diagnosis Incl. criteria
2019nCoV-301	US, Mexico	Phase 3, randomized, observer blind, placebo-controlled trial	Placebo 5 µg SARS-CoV-2 rS vaccine + 50 µg Matrix-M1 adjuvant IM injection on Days 0 and 21; antigen and adjuvant were administered as a co-formulation	Efficacy Immunogenicity Safety	SARS-CoV-2 rS: 20000 (19729) Placebo: 10000 (9853)	52.2%/47.8% 47.0 yrs	adults 18 years or older
2019nCoV-302	UK	Phase 3 randomized, observer blind, placebo-controlled trial	Placebo 5 µg SARS-CoV-2 rS vaccine + 50 µg Matrix-M1 adjuvant IM D0 & 21; antigen & adjuvant co-formulation	Efficacy Immunogenicity Safety	SARS-CoV-2 rS: 7500 (7569) Placebo: 7500 (7570)	51.6%/48.4% 55.0 yrs	Adults 18 to 84 years
2019nCoV-101, ph1	Australia	Phase 1, randomized, observer blind, placebo-controlled	Dose 1/Dose 2 (Days 0, 21) A: Placebo/ Placebo B: 25 µg+0 µg/ 25 µg+0 µg C: 5 µg+50 µg/ 5 µg+50 µg D: 25 µg+50 µg/ 25 µg+50 µg E: 25 µg+50 µg/ Placebo IM injection on Days 0 and 21; bedside mixture	Safety Immunogenicity	A: 25 (23) B: 25 (25) C: 28 (29) D: 28 (28) E: 25 (26)	Group A: 11M/12F 29 y (18-56) Group B: 12M/13F 24y (18-53) Group C: 15M/14F 27 y (18-52) Group D: 19M/9F 36 y (19-54) Group E: 9 M/17 F 31y (19-53 y)	Healthy adults 18 to 59 years of age
2019nCoV-101, ph2	Australia & US	2019nCoV-101 – Part 2	Dose 1/Dose 2 (Days 0, 21) A: Placebo/ Placebo B: 5 µg+50 µg/ 5 µg+50 µg C: 5 µg+50 µg/ Placebo D: 25 µg+50 µg/ 25 µg+50 µg E: 25 µg+50 µg/ Placebo Dose 3 (Day 189) A: Placebo B1: Placebo B2: 5 µg+50 µg C1: Placebo C2: 5 µg+50 µg D: Placebo E: Placebo IM injection on Days 0, 21, and 189; co-formulation	Immunogenicity Safety	Dose 1/Dose 2 A: 150-300 (255) B: 150-300 (258) C: 150-300 (256) D: 150-300 (259) E: 150-300 (255) Dose 3 A: 300 (0) B1: 150 (0) B2: 150 (0) C1: 150 (0) C2 150 (0) D: 300 (0) E: 300 (0)	Group A: 132M/123 F 56y (18-83) Group B: 119 M/139 F 57y (18-82) Group C: 136 M/120 F 56y (18-83) Group D: 122 M/137 F 57y (18-81) Group E: 121 M/ 134F 58y (18-84)	healthy adult participants ≥ 18 to < 85 years of age
2019nCoV-501	South Africa	Phase 2a/2b, randomized, observer blind, placebo-controlled	Placebo 5 µg SARS-CoV-2 rS vaccine + 50 µg Matrix-M1 adjuvant IM injection on Days 0 and 21; antigen and adjuvant were administered as a co-formulation	Efficacy Immunogenicity Safety	SARS-CoV-2 rS: 1480-2082 (2211) Placebo: 1480-2082 (2197)	NVX-CoV2373: 1254 M/957F 28y (18-84) Placebo: 1268 M/929 F 28y (18-83)	healthy adult HIV-negative participants and in medically stable adult HIV-positive participants 18 to 84 years of age

All studies were conducted in line with current Good Clinical Practice (GCP).

IV. 2 Pharmacokinetics

No pharmacokinetic data have been submitted for this application and none were required.

IV.3 Clinical immunogenicity

The immunogenicity data available so far were generated from study 2019nCoV-101 part 1 and 2 (dose finding study); 2019nCoV-301 and 2019nCoV-302 (pivotal studies); and 2019nCoV-501 (supportive study). Immunogenicity was assessed primarily based on circulating neutralising and spike antigen binding antibodies. A limited amount of T cell immunity data was also included in the interim report of Study 2019nCoV-101.

Bioanalytical assays

The qualification or validation reports for each bioanalytical assay have been provided. Overall, the methods were considered acceptable and fit for purpose.

Dose finding study 2019nCoV-101

Study 2019nCoV-101 is a two-part Phase I/II randomised, observer blinded, placebo-controlled study, designed to evaluate the safety and immunogenicity of NVX-CoV2373. Part one is the first-in-human trial evaluating the safety and immunogenicity of SARSCoV2 rS with or without Matrix-M adjuvant in healthy adult subjects 18 to 59 years of age at 2 sites in Australia. Part two commenced after positive results were observed following a formal analysis of the primary endpoints in Part one of the study and was designed to evaluate the safety and immunogenicity of SARS-CoV-2 rS with Matrix-M adjuvant in healthy adult subjects 18 to 84 years of age at two sites in Australia.

Both Part one and two evaluated two dose levels of SARS-CoV-2 rS (5 µg and 25 µg), which were based on the results of non-clinical studies with SARS-CoV-2 rS and on the results of clinical studies with other Novavax based nanoparticle vaccines. Both parts also evaluated a single dose level of Matrix-M adjuvant (50 µg), based on previous clinical experience with Matrix-M adjuvant.

Part 1

Subjects in Part 1 received either 1 or 2 doses of either 5 or 25 µg rS with or without 50 µg Matrix-M1 adjuvant.

Table 6: Trial design for study 2019nCoV-101 (Part 1)

Trial Vaccine Group	Number of Participants		Day 0		Day 21 (+ 5 days)	
	Randomised	Sentinel	SARS-CoV-2 rS[1] (µg)	Matrix-M1 Adjuvant (µg)	SARS-CoV-2 rS[1] (µg)	Matrix-M1 Adjuvant (µg)
A	25	–	0	0	0	0
B	25	–	25	0	25	0
C	25	3	5	50	5	50
D	25	3	25	50	25	50
E	25	–	25	50	0	0

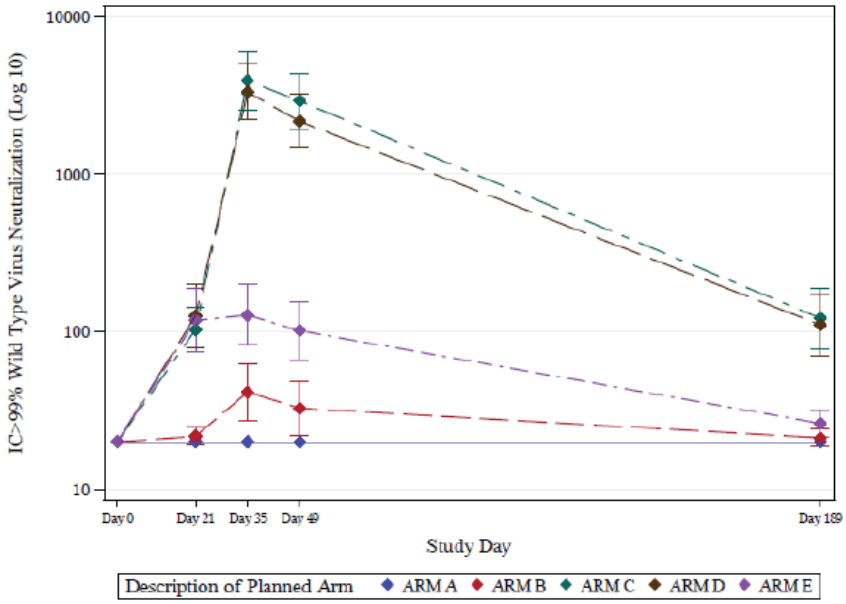
Abbreviations: SARS-CoV-2 rS = severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine.
1. Construct A (BV2373).
Note: This trial was designed to evaluate up to 2 unique constructs of SARS-CoV-2 rS (Construct A [Cohort 1] and Construct B [Cohort 2]); however, only 1 construct (Construct A) was evaluated in the trial.

The adjuvant has a dramatic boosting effect on the antibody IgG response, which it increases by a factor 10 after a first dose and 100 at the peak of the response, 2 weeks after a second dose. It also shows a significant antigen dose sparing effect since there is no notable difference in the response to 5 and 25µg of antigen after 2 doses, hence justifying the pursuit of the development with the lower dose. A strong correlation is observed between IgG and neutralising antibodies determined with a live virus assay.

The second dose of vaccine increases the IgG and neutralising antibody response by a factor of around 20, which appears necessary to achieve a magnitude that is within the range of a control panel of human convalescent serum from symptomatic and hospitalised COVID-19 patients.

After the peak, IgG levels tend to decrease slowly up to 6 months, but more rapidly so for neutralising antibodies; nevertheless, the GMTs of neutralising antibodies at 6 months are still above 100 with seroconversion rates (SCRs) around 70%.

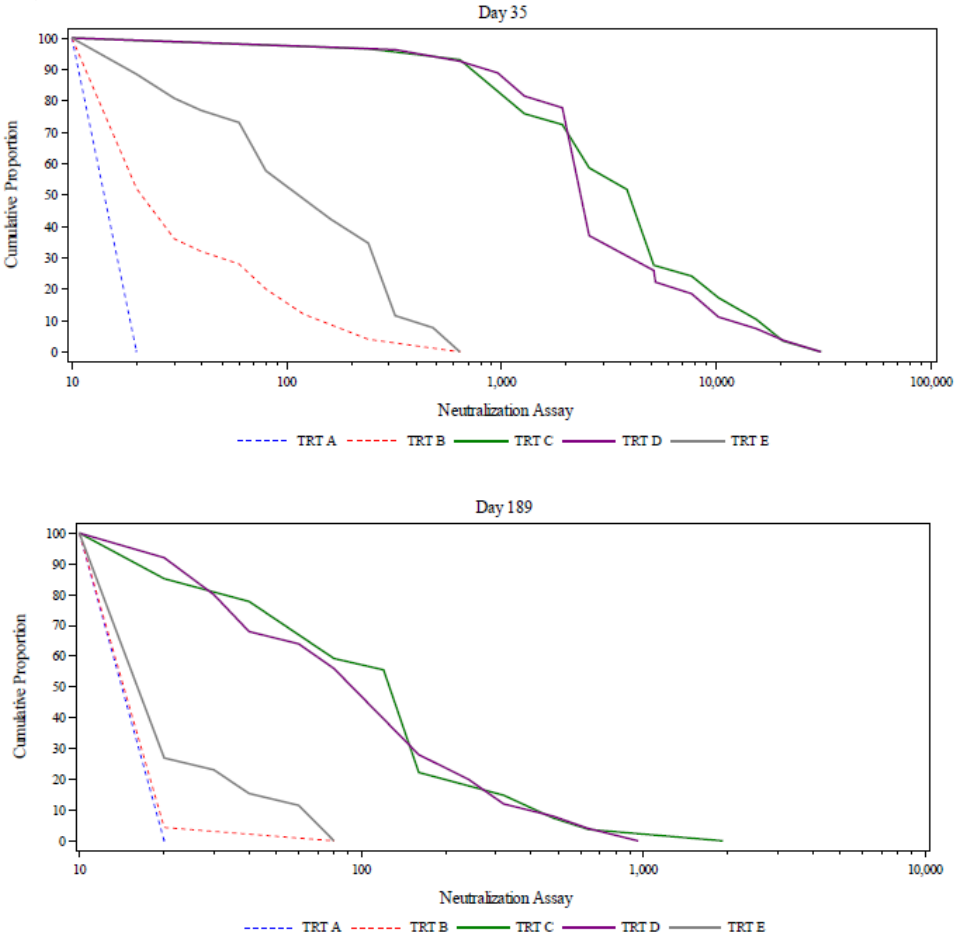
Figure 2: Part 1 – GMT* (95% CI) for Neutralising Antibodies (PP Analysis Set)



*Geometric mean titre(s)

A: placebo; B: 25 × 2; C: 5/50 × 2; D: 25/50 × 2; E: 25/50 x 1

Figure 3: Part 1 - Reverse Cumulative Distribution Function of Neutralising Antibodies (PP Analysis Set)



Part 2

Part 2 of the study was conducted in healthy males or non-pregnant females 18 to 84 years of age, inclusive, to further identify the optimal dose across age strata based on immune response at Day 35 and whether baseline immune status has an impact. The following treatment groups were included:

Table 7: Trial design for study 2019nCoV-101 (Part 2)

Treatment Group	Number of Participants	Day 0	Day 21 (−1 to +3 days)	Day 189 (±15 days)
		SARS-CoV-2 rS + Matrix-M1 Adjuvant	SARS-CoV-2 rS + Matrix-M1 Adjuvant	SARS-CoV-2 rS + Matrix-M1 Adjuvant
A	300	Placebo	Placebo	Placebo
B1	150	5 µg + 50 µg	5 µg + 50 µg	Placebo
B2	150	5 µg + 50 µg	5 µg + 50 µg	5 µg + 50 µg
C1	150	5 µg + 50 µg	Placebo	Placebo
C2	150	5 µg + 50 µg	Placebo	5 µg + 50 µg
D	300	25 µg + 50 µg	25 µg + 50 µg	Placebo
E	300	25 µg + 50 µg	Placebo	Placebo

Abbreviations: AUS = Australia; HERC = human research ethics committee; IRB = institutional review board; SARS-CoV-2 rS = severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine; USA = United States of America.

Overall, the interim results from the larger study population in part 2 support the findings in Part 1 and provide further support for the inclusion of the adjuvant and administration of a second dose, with again no apparent advantage for 25 vs. 5 μg antigen doses in the adjuvanted formulations.

Of the 1,198 participants in the PP-Immunogenicity Analysis set, 30 (2.5%) were seropositive at baseline. IgG levels for the two-dose regimens in seropositive participants were more than double those reported for all participants regardless of baseline serostatus.

The antibody response in the ≥ 60-year olds is about half that in younger adults, but the seroconversion rate after 2 doses is > 96% regardless of age. A similar pattern is seen with the neutralising antibody responses.

Cellular response (Part 1 and 2)

Consistent with the antibody response, adjuvant is crucial for induction of an antigen specific T cell response and a second dose of vaccine is needed to achieve a robust response. Elispot and Intracellular cytokine staining assays show an increase from baseline in Th1 cytokine-producing T cells (IFNγ, TNFα, IL-2) as well as Th2 cytokine-producing T cells (IL-5, IL-13). Overall, a mixed Th1/Th2 profile is observed, which can be considered skewed toward a Th1 response.

Main studies 2019nCoV-301, 302 and 501

The clinical phase 3 data confirm that the vaccine produces a robust immune response, and the studied two dose schedule resulted in seroconversion in almost all participants. As expected, immune responses were somewhat lower in adults ≥ 65 years of age compared with younger adults. In subjects that were seropositive at baseline, the 2-dose regimen resulted in a markedly increased humoral immune response.

An exploratory authorised seasonal influenza co-administration substudy was conducted as part of study 302 in the first approximately 400 participants who met the additional inclusion criteria for this study (i.e., participant had not received a current season influenza vaccine, had no contraindication to the specific vaccine to be administered in the study, and had no prior history of allergy or severe reaction to seasonal influenza vaccines). Licensed inactivated seasonal influenza vaccines were co-administered to participants on the same day as Dose 1 of NVX-CoV2373 (n = 217) or placebo (n = 214) in the opposite deltoid muscle of the arm. An unadjuvanted quadrivalent influenza vaccine (Flucelvax, Seqirus) was given to those 18 to 64 years of age, and an adjuvanted trivalent influenza vaccine (Fluad, Seqirus) was given to those ≥ 65 years of age, in compliance with UK recommendations.

Co-administration resulted in no change to influenza vaccine immune responses as measured by hemagglutination inhibition (HAI) assay. A 30% reduction in antibody responses to NVX-CoV2373 was noted as assessed by an anti-spike IgG assay with seroconversion rates similar to participants who did not receive concomitant influenza vaccine. SARS-CoV-2 neutralising antibody responses for the influenza substudy participants were not investigated by the applicant. Whilst a few cases of PCR-confirmed symptomatic COVID-19 occurred in the immunogenicity subset (n=10 in total, 2 in the active arm and 8 in the placebo arm) the number is considered too small to make any clear conclusions on any clinical impact of the reduced immune response and the impact of this is therefore considered unknown.

In the supportive study 501 a limited amount of immunogenicity data is available in the interim report in participants with medically stable HIV. In HIV seropositive participants that were seropositive for SARS-CoV-2 at baseline, the neutralising antibody GMTs for HIV were comparable to those seen for HIV-negative participants. In HIV positive participants that were seronegative for SARS-CoV-2 at baseline, neutralising antibody responses were somewhat lower than those seen in HIV negative participants, but the seroconversion rate remained high (98%).

IV.4 Clinical efficacy

Clinical efficacy data are available from two pivotal phase 3 trials, 2019nCoV-301 and 2019nCoV-302, and a supportive phase 2 trial, 2019nCoV-501.

Pivotal study 2019nCoV-301

Methods

Study 1 is an ongoing Phase 3, multicentre, randomised, observer-blinded, placebo-controlled study in participants 18 years of age and older in United States and Mexico. Upon enrolment, participants were stratified by age (18 to 64 years and ≥ 65 years) and assigned in a 2:1 ratio to receive NVX-CoV2373 or placebo.

Enrolment of adults completed in February 2021. Participants will be followed for up to 24 months after the second dose for assessments of safety, and efficacy against COVID-19. The trial also includes a blinded crossover period in which subjects were re-vaccinated with 2 injections of alternative study product 21 days apart following accrual of sufficient efficacy and safety data to support application for Emergency Use Authorization (EUA) by the US Food and Drug Administration (FDA). The blinded crossover period commenced on 20 April 2021. All participants were offered the opportunity to continue to be followed in the study.

Study participants

The trial included healthy male or female participants aged 18 years and older, who did not have a history of laboratory-confirmed (by PCR or serology to SARS-CoV-2) COVID-19 infection at any time prior to randomisation. The trial focussed on enrolment of participants at high risk of complications due to COVID-19 due to underlying coming comorbidities or living/working conditions. Participants with stable chronic medical conditions were not excluded unless participants were immunocompromised (iatrogenic or pathogenic), had an autoimmune disease/condition or a current diagnosis of or treatment for cancer. Further, pregnant and breastfeeding women were also excluded from participation. Additionally, normal inclusion and exclusion criteria appropriate for a vaccine trial were in place.

Statistical analysis

The primary efficacy analysis set was defined as the per protocol efficacy population (PP-EFF), consisting of all randomised participants without major protocol deviations that occurred before the first COVID-19 positive episode, who are seronegative (for SARS-CoV-2) at baseline and do not have a laboratory confirmed current SARS-CoV-2 infection with symptom onset up to 6 days after the second dose, and who have received both doses less than 45 days apart.

Analysis of primary efficacy endpoint

Vaccine Efficacy of PCR-Confirmed SARS-CoV-2 Positivity with Symptomatic Mild, Moderate, or Severe COVID-19 from 7 days after Second Vaccination in the initial vaccination period in in participants serologically negative (to SARS-CoV-2) at baseline.

The same analysis method was used as was used for the primary analysis in trial 302 (a Poisson regression model with robust variance). The primary efficacy analysis was conducted with data collected up to the blinded crossover. The participants' follow-up time ended after reaching the first occurrence of any of the following events: a positive endpoint definition, the participant terminated from the study early, the participant died, the participant completed the study as scheduled, the study was stopped early, start of any PCR-confirmed illness episode, any positive PCR result after screening, participant entered the blinded crossover, occurrence of major protocol deviation, the participant was unblinded to treatment assignment, or database extract date.

The analysis of the primary efficacy endpoint included all data prior to the blinded crossover which was initiated following the accumulation of the median 2-month (60 days) safety follow-up.

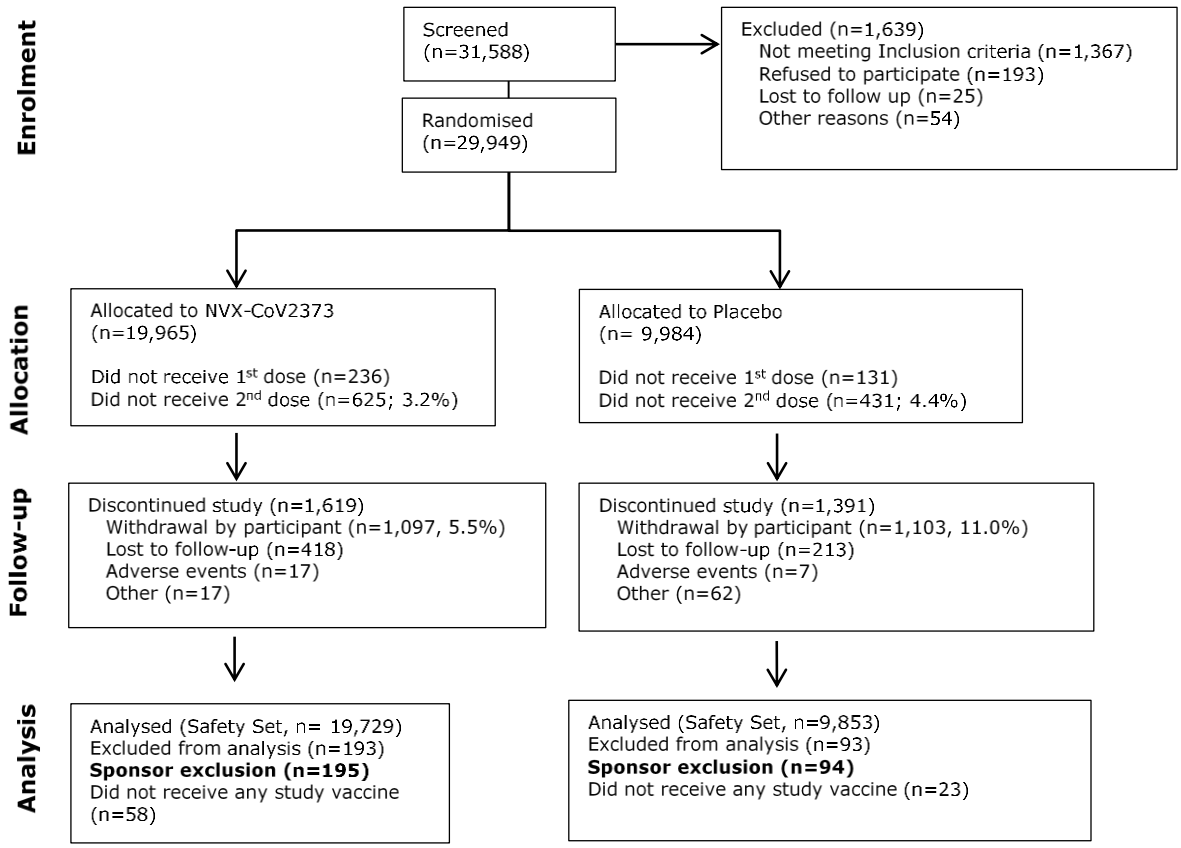
The result of the primary analysis was considered positive if the lower bound of the 2-sided 95% confidence interval for VE was greater than 30%. Based upon the number of primary efficacy endpoints planned for analysis, a lower bound of more than 30% corresponds with a vaccine efficacy point estimate of at least 50%.

Results

An interim study report has been provided that describes the efficacy and safety results in adults following the initial set of vaccinations until each participant's first blinded crossover vaccination or as of the data cut-off date of 31 May 2021. The interim report excludes data from the blinded adult crossover period.

<u>Study population</u>

Figure 4: Study participant flow



A higher percentage of subjects discontinued the study in the placebo group (8.1%) compared with the NVX-CoV2373 group (3.9%). The most frequent reasons for study discontinuation were ‘withdrawal by participant’ and ‘Lost to follow-up’. The percentage of subjects that discontinued due to an adverse event was very low and balanced between the two treatment groups.

Approximately 18% of participants were unblinded to study treatment assignment during the course of the study. In almost all cases, the reason was to receive an authorised vaccine. There was an imbalance between treatment groups with a higher proportion of placebo recipients (23.4%) requesting unblinding than vaccine recipients (15.2%), observed for most clinical sites. No obvious association between reactogenicity profile and request for unblinding has been observed.

Overall, the demographics and baseline characteristics were well balanced between the 2 treatment groups.

Table 8: Demographics and baseline characteristics (PP-EFF analysis set)

Parameter	NVX-CoV2373 N = 17312	Placebo N = 8140	Total N = 25452
Age (years)			
Mean (SD)	46.3 (14.89)	46.6 (14.78)	46.4 (14.86)
Median	47.0	47.0	47.0
Min, max	18 - 95	18 - 90	18 - 95
Age group, n (%)			
18 to ≤ 64 years	15264 (88.2)	7194 (88.4%)	22458 (88.2)
≥ 65 years	2048 (11.8)	946 (11.6%)	2994 (11.8)
Sex, n (%)			
Male	9050 (52.3)	4131 (50.7)	13181 (51.8)
Female	8262 (47.7)	4009 (49.3)	12271 (48.2)
Race, n (%)			
White	13140 (75.9)	6184 (76.0)	19324 (75.9)
Black or African American	1893 (10.9)	900 (11.1)	2798 (11.0)
American Indian or Alaska Native	1074 (6.2)	498 (6.1)	1572 (6.2)
Asian	761 (4.4)	366 (4.5)	1127 (4.4)
Multiple	293 (1.7)	132 (1.6)	425 (1.7)
Native Hawaiian or Other Pacific Islander	47 (0.3)	10 (0.1)	57 (0.2)
Not reported	104 (0.6)	45 (0.6)	149 (0.6)
Ethnicity, n (%)			
Not Hispanic or Latino	13538 (78.2)	6379 (78.4)	19917 (78.3)
Hispanic or Latino	3733 (21.6)	1751 (21.5)	5484 (21.5)
Not reported	22 (0.1)	9 (0.1)	31 (0.1)
Unknown	19 (0.1)	1 (< 0.1)	20 (0.1)
BMI category, n (%)			
Underweight (< 18.0 kg/m^2)	126 (0.7)	51 (0.6)	177 (0.7)
Normal (18.0 – 24.9 kg/m^2)	5061 (29.2)	2327 (28.6)	7388 (29.0)
Overweight (25.0 – 29.9 kg/m^2)	5649 (32.6)	2664 (32.7)	8313 (32.7)
Obese (≥ 30.0 kg/m^2)	6400 (37.0)	3070 (37.7)	9470 (37.2)

Occupation			
Currently working	11924 (68.9)	5574 (68.5)	17498 (68.7)
Working in close proximity to others	4436 (25.6)	2063 (25.3)	6499 (25.5)
Student attending school in person	1021 (5.9)	436 (5.4)	1457 (5.7)
In-person schooling/currently working/ working in close proximity to others, n (%)	**13,267 (76.6)**	**6200 (76.2)**	**19,467 (76.5)**
Days/week at workplace, n (%)			
0 days/week	2821 (16.3)	1405 (17.3)	4226 (16.6)
1 day/week	873 (5.0)	371 (4.6)	1244 (4.9)
2 – 4 days/week	3022 (17.5)	1442 (17.7)	4464 (17.5)
≥ 5 days/week	5193 (30.0)	2349 (28.9)	7542 (29.6)
PPE used by people at workplace, n (%)	**9027 (52.1)**	**4160 (51.1)**	**13,187 (51.8)**
Living situation, mean (SD)			
Number of people living with participant	2.0 (2.69)	1.9 (1.94)	1.9 (2.48)
Number of co-habitants under 18 years	0.6 (1.01)	0.6 (1.01)	0.6 (1.01)
Number of co-habitants 18 to 64 years	1.2 (2.50)	1.2 (1.65)	1.2 (2.26)
Number of co-habitants ≥ 65 years	0.2 (0.45)	0.2 (0.45)	0.2 (0.45)
Lifestyle, n (%)			
History of smoking/vaping	5319 (30.7)	2494 (30.6)	7813 (30.7)
Currently smoking/vaping	2603 (15.0)	1210 (14.9)	3813 (15.0)
Country, n (%)			
United States	16294 (94.1)	7638 (93.8)	23932 (94.0)
Mexico	1018 (5.9)	502 (6.2)	1520 (6.0)
High-risk adults[1], n(%)			
Yes	16,493 (95.3)	7737 (95.0)	24,230 (95.2)
No	819 (4.7)	403 (5.0)	1222 (4.8)
Comorbidities, n (%)			
Obesity (BMI ≥ 30 kg/m^2)	6400 (37.0)	3070 (37.7)	9470 (37.2)
Chronic lung disease	2442 (14.1)	1218 (15.0)	3660 (14.4)
Diabetes mellitus type 2	1303 (7.5)	1303 (7.5)	677 (8.3)
Cardiovascular disease	191 (1.1)	191 (1.1)	91 (1.1)
Chronic kidney disease	109 (0.6)	109 (0.6)	50 (0.6)

The age range of participants was 18-95 years with a median age of 47 years. Approximately 11.8% of participants were ≥ 65 years of age. Approximately half the participants were male, while the majority (75.9%) were White (78.2%) and located in the United States (94.0%). The majority of participants were overweight or obese (69.9%), with more than a third being obese (37.2%). Most participants (95.2%) were categorized as high-risk adults for acquiring or experiencing complications of COVID-19.

Baseline characteristics were similar between the PP-EFF and safety analysis sets. In the safety analysis set, baseline serostatus was balanced between the 2 treatments groups with most participants seronegative at baseline (NVX-CoV2373: 93.7%, placebo: 93.1%).

Overall, data analysis sets were generally well balanced between the NVX-CoV2373 and placebo groups.

Table 9: Analysis sets (All randomised participants)

Analysis Sets	NVX-CoV2373 N = 19965	Placebo N = 9984	Total N=29949
ITT	19965 (100)	9984 (100)	29949 (100)
FAS	19714 (98.7)	9868 (98.8)	29582 (98.8)
Safety	19729 (98.8)	9853 (98.7)	29582 (98.8)
PP-EFF	17312 (86.7)	8140 (81.5)	25452 (85.0)
PP-EFF2	18438 (92.4)	8740 (87.5)	27178 (90.7)

Primary efficacy endpoint

Results are presented for the primary efficacy analysis which was triggered when 60-day median safety follow-up was achieved. The data cut-off for this analysis was 19 April 2021, at which point there were 77 cases eligible for the primary endpoint.

The study has successfully achieved its primary objective. The vaccine efficacy point estimate was **90.4% (95% CI: 82.9, 94.6)** with a lower bound of the 95% confidence interval >30%. As the point estimate was above 50% and the confidence interval lower bound above 30%, efficacy was also shown in line with the target profile outlined by WHO for COVID-19 vaccines.

Table 10: Vaccine Efficacy against PCR-Confirmed Symptomatic Mild, Moderate, or Severe COVID-19 with Onset from at Least 7 Days after Second Vaccination in Serologically Negative Adult Participants (PP-EFF Analysis Set)

	NVX-CoV2373 (N=17312)	Placebo (N=8140)
Cases (%)*	14 (0.1)	63 (0.8)
Median surveillance time (days)	64	58
Mild	14	49
Moderate	0	10
Severe	0	4
Incidence rate (cases per 1,000 participant years)	3.26	34.01
Vaccine Efficacy (%)	90.40	
95% CI	(82.88, 94.62)	
p-value (for test of VE > 30%)	$p < 0.001$	

*Does not include cases which were PCR positive without symptoms meeting illness criteria

Subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates for male and female participants and racial groups, and across participants with medical comorbidities associated with high risk of severe COVID-19.

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

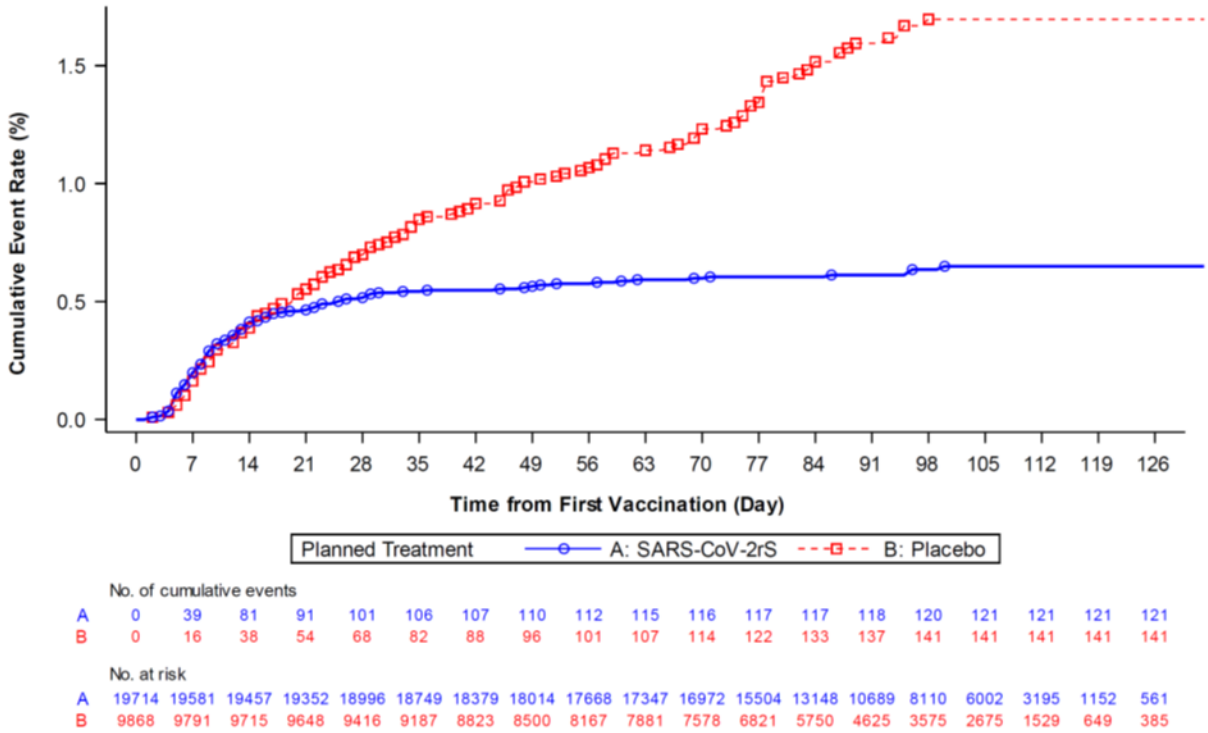
Severe cases and hospitalisations

No cases of severe COVID-19 were reported in the 17,312 NVX-CoV2373 participants compared with 4 cases of severe COVID-19 reported in the 8,140 placebo recipients in the PP-EFF analysis set. No cases in either treatment group required hospitalisation.

Protection after first dose

The figure below displays cumulative incidence for the first COVID-19 occurrence after Dose 1 among all vaccinated participants. Disease incidence is similar for the vaccine and placebo groups until around day 14-21 after dose 1, at which point the curves diverge, suggesting onset of protection from this point.

Figure 5: Cumulative Incidence Curve of PCR-Confirmed Symptomatic Mild, Moderate, or Severe COVID-19 with Onset from First Vaccination in Adult Participants Regardless of Baseline Serostatus (Full Analysis Set)



Pivotal study 2019nCoV-302

Methods

Study 2 is an ongoing Phase 3, multicentre, randomised, observer-blinded, placebo-controlled study in participants 18 to 84 years of age in the United Kingdom. Upon enrolment, participants were stratified by age (18 to 64 years; 65 to 84 years) and assigned in a 1:1 ratio to receive to receive NVX-CoV2373 or placebo.

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

COVID-19. Following permission by regulatory bodies based on achieving the primary efficacy endpoint and an acceptable safety profile, the study includes a blinded crossover period beginning three months following the second dose. Participants who initially received NVX-CoV2373 would be revaccinated with two doses of placebo given 21 days apart. Similarly, participants who initially received placebo would be revaccinated with 2 doses of NVX-CoV2373. The blinded crossover period commenced on 29 March 2021.

Study participants

As for study 301, the trial focussed on enrolment of participants at high risk of complications due to COVID-19 due to underlying coming comorbidities or living/working conditions. The main inclusion/exclusion criteria were also generally similar to those for study 302.

Statistical analysis

As in study 301, the primary analysis was conducted in the PP-EFF population. The analysis was performed based only on the data generated prior to the blinded crossover.

Analysis of primary efficacy endpoint

First occurrence of virologically confirmed, symptomatic mild, moderate, or severe COVID-19 with onset from at least 7 days after second study vaccination in the initial set of vaccinations in participants serologically negative (to SARS-CoV-2) at baseline.

A Poisson regression model with robust variance (Zou 2004) was used as the primary efficacy analysis model to estimate the relative risk (RR) of the incidence of SARS-CoV-2 virologically-confirmed primary symptomatic COVID-19 between the NVX-CoV2373 and placebo groups. The model contained the terms of treatment group, age group (18 to 64 years / 65 to 84 years) and region (pooled sites). The pooling of sites into regions was determined and documented prior to breaking the blind. The natural log of the surveillance time was used as an offset variable in the model to adjust for volunteers having different follow up times.

Vaccine efficacy (VE), which is the incidence of infection in the vaccine group relative to the incidence of infection in the control group expressed as a percentage, was calculated as VE (%) = (1 – RR) × 100. The VE, and its corresponding 2-sided (1-α) % confidence interval (CI), will be estimated from the model. The one-sided p-value for the test of VE ≤ 30% was also calculated from the model.

The Clopper-Pearson exact binomial method was used in if there was a low number of events, or if the modified Poisson regression model did not converge (i.e., zero counts in 1 study vaccine group or stratum).

An interim analysis and a final analysis were planned. The interim analysis was planned for when approximately 50 COVID-19 cases fulfilling criteria for the primary endpoint as described above had occurred. The final analysis was planned for when approximately 100 cases had occurred.

The interim and final analyses for the primary objective in the PP-EFF population were carried out at the overall one-sided Type I error rate of 0.025. The nominal 1-sided alpha was planned to be 0.01550 at the interim analysis and 0.01387 at the final analysis. If an unplanned additional interim analysis if the timing of a planned analysis is modified, the Lan-

DeMets alpha-spending function was to be used to adjust the nominal alphas to maintain the overall one-sided type I error at 0.025.

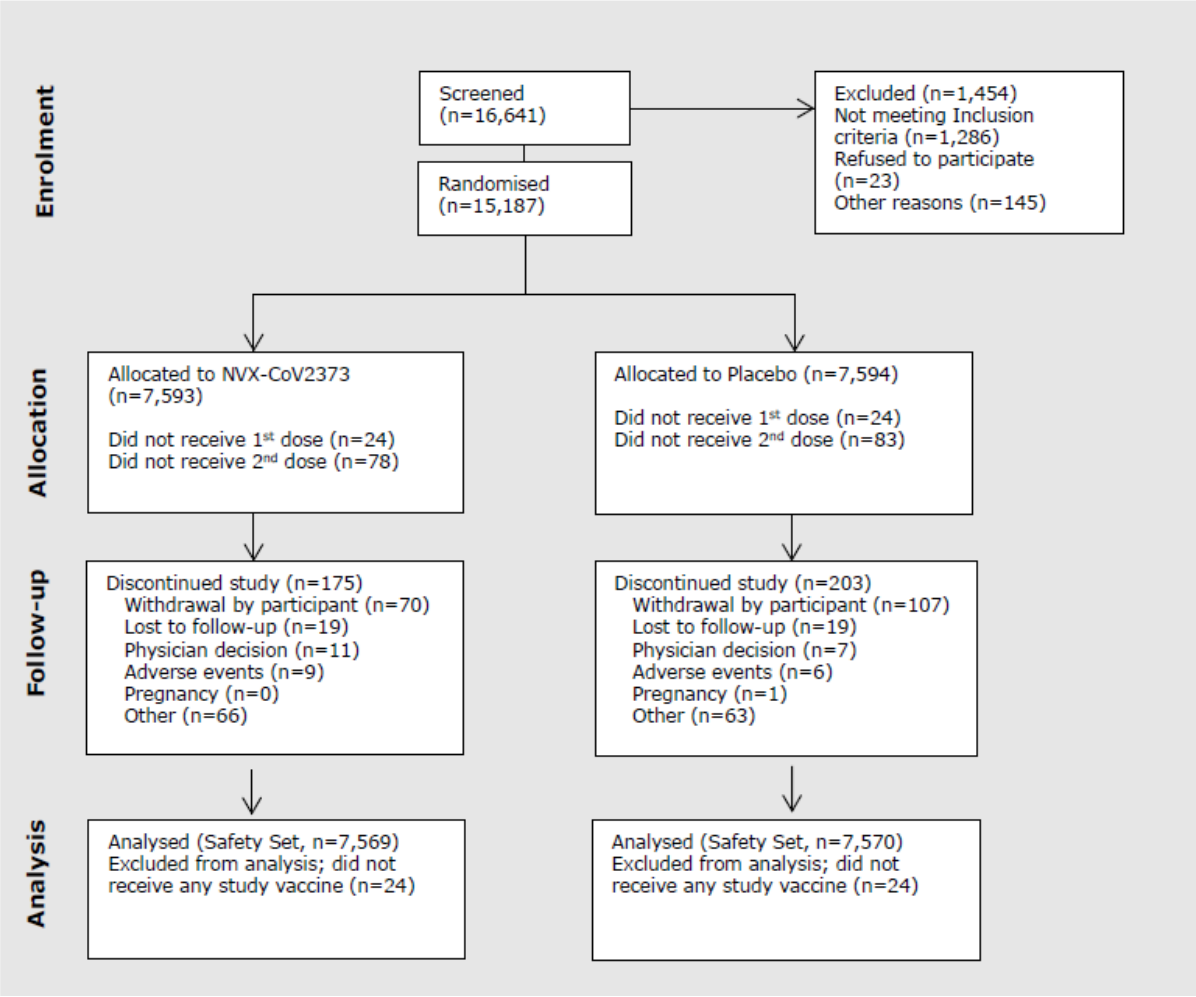
The result of the primary analysis was considered positive at either the interim or final analysis if the lower bound of the alpha adjusted confidence interval for VE was greater than 30%.

Results

An interim study report has been provided. The data cut-off date of the interim efficacy analysis was 10 January 2021, the data cut-off date for the final efficacy analysis was 29 January 2021, and the data cut-off date for all other analyses was 23 February 2021.
The interim report excludes data from the blinded adult crossover period.

Study population

Figure 6: Study participant flow



The percentage of subjects that discontinued the study is low and balanced between the vaccine (2.3%) and placebo (2.7%) arms with very few subjects discontinuing due to an adverse event.

Approximately one-third of participants in both study arms were unblinded to study vaccine assignment during the course of the study. In almost all subjects this was because they

wished to receive an approved vaccine. The vast majority of unblinded subjects continue to be followed up for safety.

Overall, the demographics and baseline characteristics in the primary analysis population (PP-EFF) are well balanced across the vaccine and placebo arms.

Table 11: Demographics and baseline characteristics (PP-EFF analysis set)

Parameter	NVX-CoV2373 N = 7020	Placebo N = 7019	Total N = 14039
Age (Years)			
Mean (SD)	53.4 (14.81)	53.4 (14.84)	53.4 (14.82)
Median	56.0	56.0	56.0
Min, max	18, 84	18, 84	18, 84
Age group, n (%)			
18 to 64 years	5067 (72.2)	5062 (72.1)	10129 (72.1)
65 to 84 years	1953 (27.8)	1957 (27.9)	3910 (27.9)
Sex, n (%)			
Male	3609 (51.4)	3629 (51.7)	7238 (51.6)
Female	3411 (48.6)	3390 (48.3)	6801 (48.4)
Race, n (%)			
White	6625 (94.4)	6635 (94.5)	13260 (94.5)
Asian	201 (2.9)	212 (3.0)	413 (2.9)
Multiple	70 (1.0)	59 (0.8)	129 (0.9)
Black or African American	26 (0.4)	26 (0.4)	52 (0.4)
Other	4 (<0.1)	6 (<0.1)	10 (<0.1)

Parameter	NVX-CoV2373 N = 7020	Placebo N = 7019	Total N = 14039
American Indian or Alaska Native	4 (<0.1)	0	4 (<0.1)
Native Hawaiian or Other Pacific Islander	1 (<0.1)	0	1 (<0.1)
Not Reported	85 (1.2)	79 (1.1)	164 (1.2)
Missing	4	2	6
Ethnicity, n (%)			
Not Hispanic or Latino	6142 (87.5)	6187 (88.1)	12329 (87.8)
Hispanic or Latino	63 (0.9)	51 (0.7)	114 (0.8)
Not Reported	684 (9.7)	639 (9.1)	1323 (9.4)
Unknown	127 (1.8)	138 (2.0)	265 (1.9)
Missing	4	4	8
BMI (kg/m^2)			
n	6844	6847	13691
Mean (SD)	27.51 (5.373)	27.72 (5.733)	27.62 (5.557)
Median	26.70	26.80	26.70
Min, max	3.4, 64.5	4.9, 87.4	3.4, 87.4
BMI group (kg/m^2), n (%)			
≤ 30	5060 (72.1)	4984 (71.0)	10044 (71.5)
> 30	1784 (25.4)	1863 (26.5)	3647 (26.0)
Missing	176	172	348
Day 0 PCR, n (%)			
Positive (+)	0	0	0
Negative (-)	6621 (94.3)	6611 (94.2)	13232 (94.3)
Missing	399	408	807
Day 0 SARS-CoV-2 Serostatus[1], n (%)			
Positive	0	0	0
Negative	6964 (99.2)	6944 (98.9)	13908 (99.1)
Missing	56	75	131
Comorbidity status[2], n (%)			
Yes	3117 (44.4)	3143 (44.8)	6260 (44.6)
No	3903 (55.6)	3876 (55.2)	7779 (55.4)

There are similar percentages of males and females. Subjects range from 18-84 years of age, with a median age of 56. Approximately 28% of subjects were between 65 and 84 years of age. The vast majority of subjects were white (94.5%). Subjects with a comorbidity are well represented in the population (44.6%) and 26% of subjects are obese (BMI >30).

With the expected exception of Day 0 PCR and SARS-CoV-2 serostatus, the demographics and baseline characteristics are similar and well balanced in the ITT analysis set. Approximately 4% of subjects in the vaccine and placebo arms were seropositive at baseline in the ITT population.

Overall, data analysis sets were generally well balanced between the NVX-CoV2373and placebo groups.

Table 12: Analysis sets (All randomised subjects analysis set)

Analysis Sets	NVX-CoV2373	Placebo	Total
All randomized subjects analysis set	7593 (100.0)	7594 (100.0)	15187 (100.0)
Safety analysis set	7569 (99.7)	7570 (99.7)	15139 (99.7)
ITT analysis set	7569 (99.7)	7570 (99.7)	15139 (99.7)
Anti-S protein serology subset	502 (6.6)	497 (6.5)	999 (6.6)
Neutralization assay subset	500 (6.6)	497 (6.5)	997 (6.6)
Cell-mediated assay subset	224 (3.0)	223 (2.9)	447 (2.9)
Seasonal influenza vaccine substudy	217 (2.9)	214 (2.8)	431 (2.8)
PP-EFF analysis set	7020 (92.5)	7019 (92.4)	14039 (92.4)
PP-IMM anti-S protein serology subset	414 (5.5)	417 (5.5)	831 (5.5)
PP-IMM neutralization assay subset	381 (5.0)	380 (5.0)	761 (5.0)
Solicited AE safety subset analysis set	1364 (18.0)	1350 (17.8)	2714 (17.9)
Seasonal influenza vaccine substudy set	217 (2.9)	214 (2.8)	431 (2.8)

Primary efficacy endpoint

Results are presented for the interim efficacy analysis based on a data cut-off of 10 January 2021 and for the final efficacy analysis based on a data-cut-off of 29 January 2021. There were 62 cases observed at the time of the interim analysis, which is close to the approximately 50 planned. The pre-specified 1-sided alpha level of 0.01550 was used, meaning inference was based upon 2-sided 96.9% confidence intervals. As the interim analysis was positive, the final analysis is not formally inferential and the full 1-sided 2.5% alpha could be used to present the results at this analysis along with 2-sided 95% confidence intervals.

Confirmatory interim analysis

The study has successfully achieved its primary objective. The vaccine efficacy point estimate was **89.3% (alpha adjusted 96.9% CI: 73.0, 95.8)** with an alpha adjusted lower bound of the confidence interval >30%. As the point estimate was above 50% and the confidence interval lower bound above 30%, efficacy was also shown in line with the target profile outlined by WHO for COVID-19 vaccines.

Table 13: Interim Analysis of Vaccine Efficacy against PCR-Confirmed Symptomatic Mild, Moderate, or Severe COVID-19 with Onset from at Least 7 Days after Second Vaccination in Serologically Negative Adult Participants (PP-EFF Analysis Set)

	NVX-CoV2373 (N=7016*)	Placebo (N=7033*)
Cases (%)	6 (<0.1)	56 (0.8)
Median surveillance time (days)	39	39
Incidence rate (cases per 1,000 participant years)	5.06	47.30
Vaccine Efficacy (%)	89.3	
Alpha adjusted 96.9% CI	(73.0, 95.8)	
p-value (for test of VE > 30%)	p < 0.001	
95% CI	(75.2, 95.4)	

*Includes participants ongoing in the study who had not reached the surveillance period at the time of data cut-off for the interim analysis

Final primary efficacy analysis

The efficacy first demonstrated at the interim analysis was confirmed by the results from the final analysis. The vaccine efficacy point estimate was **89.7% (95% CI: 80.2, 94.6).**

Table 14: Final Analysis of Vaccine Efficacy against PCR-Confirmed Symptomatic Mild, Moderate, or Severe COVID-19 with Onset from at Least 7 Days after Second Vaccination in Serologically Negative Adult Participants (PP-EFF Analysis Set)

	NVX-CoV2373 (N=7020)	Placebo (N=7019)
Cases (%)*	10 (0.1)	96 (1.4)
Mild	1	28
Moderate	9	63
Severe	0	5
Median surveillance time (days)	56	54
Incidence rate (cases per 1,000 participant years)	6.53	63.43
Vaccine Efficacy (%)	89.7	
95% CI	(80.2, 94.6)	
p-value (for test of VE > 30%)	$p < 0.001$	

*There were 3 cases (1 on NVX-CoV2373, 2 on placebo) which were PCR positive without symptoms meeting illness criteria

Subgroup analyses of the final analysis of the primary efficacy endpoint showed similar efficacy point estimates for male and female participants, between elderly (≥ 65 years) and younger individuals (18 to 64 years), and across participants with medical comorbidities associated with high risk of severe COVID-19.

Efficacy by strain

At the time of enrolment in study 302, the B.1.17 (Alpha) variant was circulating in the UK. Strain data was available for 95 of the 106 endpoint cases, of which 66 (69%) were identified as the Alpha variant. PCR results of the final analysis by SARS-CoV-2 strain showed estimated VEs of NVX-CoV2373 to prevent symptomatic mild, moderate, or severe COVID-19 in baseline seronegative (to SARS-CoV-2) participants were 86.3% (95% CI: 71.3, 93.5) for the UK (Alpha) variant B.1.1.7 and 96.4% (95% CI: 73.8, 99.5) for the ancestral (Wuhan) strain.

Severe cases and hospitalisations

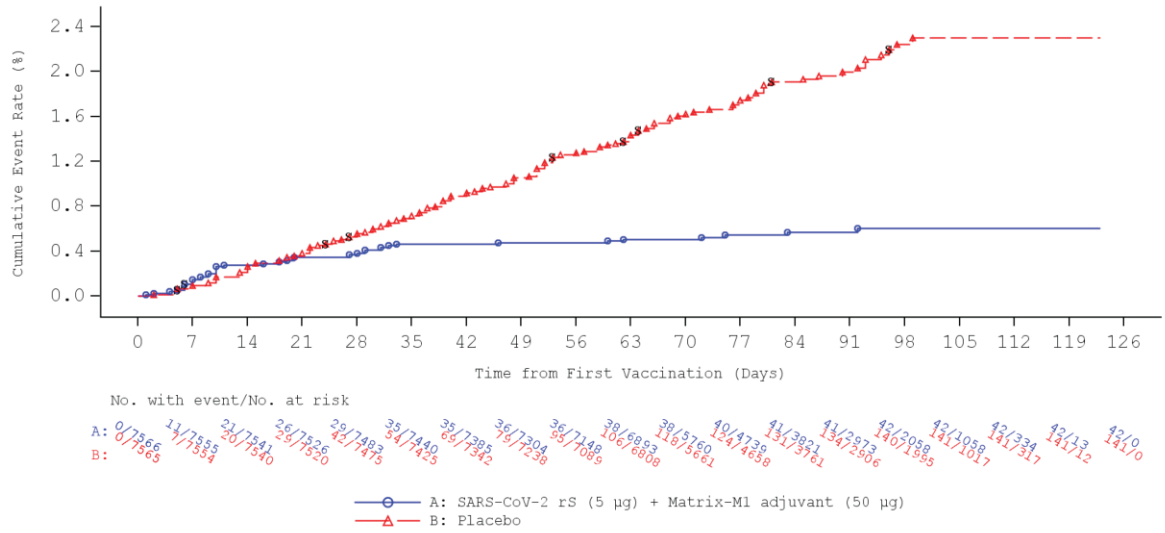
No cases of severe COVID-19 were reported in NVX-CoV2373 participants compared with 5 cases reported in placebo recipients in the PP-EFF analysis set. One case in the placebo group required hospitalisation.

Protection after first dose

The figure below displays cumulative incidence for the first COVID-19 occurrence after Dose 1 among all vaccinated participants. Disease incidence is similar for the vaccine and placebo groups until around day 21 after dose 1, at which point the curves diverge,

suggesting onset of protection from this point.

Figure 7: Cumulative Incidence Curve of PCR-Confirmed Symptomatic Mild, Moderate, or Severe COVID-19 with Onset from First Vaccination in Adult Participants Regardless of Baseline Serostatus (ITT Analysis Set)



Supportive study 2019nCoV-501

Methods

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

Enrolment was completed in November 2020. Participants were randomised 1:1 to receive NVX-CoV2373 or placebo. At 6 months after the last vaccination in the initial vaccination period, participants were to be given the option to enter into the crossover vaccination period. The duration of the study, excluding screening, was to be approximately 12 months after the last vaccination in the initial vaccination period.

The primary endpoint was PCR-confirmed symptomatic mild, moderate, or severe COVID-19 in serologically naïve (to SARS-CoV-2) healthy HIV-negative and medically stable HIV-positive adult participants, analysed overall, with a lower bound of the 95% confidence interval for VE above 0, from 7 days after the second vaccine dose until the endpoint-driven efficacy analysis is triggered by the occurrence of a prespecified number of blinded endpoints across the 2 study vaccine arms and/or at prespecified time points during the initial vaccination period. The pre-specified success criteria would not satisfy the WHO criteria but would demonstrate that the vaccine is better than placebo.

Results

Study population

In total, 4,419 subjects were randomised (4,173 HIV-negative and 246 HIV-positive). At the cut-off date, 4,325 (97.9%) were continuing in follow-up and 94 (2.1%) had discontinued the study.

Demographic and baseline characteristics were well balanced between the NVX-CoV2373 and placebo groups, overall and by HIV status. Of participants, 94% were HIV-negative. Median age was 28 years (range: 18 to 84 years); 40% were female; 91% were Black/African American; 2% were White; 3% were multiple races, 1% were Asian; and 2% were Hispanic or Latino. At baseline, 34.1% of participants were seropositive for SARS-CoV-2. For HIV positive participants, the majority (63.9%) had no co-morbidities. Median baseline CD4 level was 738 cells/μL (range 80 to 2,076 cells/μL) and median baseline HIV viral load was 63.5 copies/mL (range 20 to 735 copies/mL).

The PP-EFF was the main population for the efficacy analysis. The PP-EFF Analysis Set included 2,770 (62.7%) participants, with 1,408 (63.6%) in the NVX-CoV2373 group and 1,362 (61.7%) in the placebo group. The main reasons for exclusion from the PP-EFF analysis set were positive PCR test or PCR-confirmed illness episode before 7 days after second study vaccination (n=1,488, 33.7%) and missed 1 dose of study vaccine (n=148, 3.3%).

Primary efficacy endpoint

Results are presented for the official event-driven analysis based on a data cut-off of 18 January 2021, at which point there were 44 cases eligible for the primary endpoint, which is in the range of 23-50 events that was planned. Results are also presented for the complete analysis as of 23 February 2021 when there were 147 cases.

Official event-driven analysis

The vaccine efficacy point estimate was 49.4% (95% CI: 6.1, 72.8). The lower bound of the 95% confidence interval for VE from 7 days after dose 2 was > 0% so the study is positive by the pre-specified statistical criteria and has demonstrated better VE than placebo. As the lower bound was not > 30% and the point estimate was not greater than 50% efficacy consistent with WHO criteria was not shown.

Complete analysis

Table 15*:* Vaccine Efficacy of PCR-Confirmed SARS-CoV-2 Positivity with Symptomatic Mild, Moderate, or Severe COVID-19 from 7 Days after Second Vaccination Overall and in Healthy HIV-Negative and Medically Stable HIV-Positive Participants Stratified by Baseline Serostatus and Regardless of Baseline Serostatus (PP-EFF and Second PP-EFF Analysis Sets) – Complete Analysis

	NVX-CoV2373	Placebo	VE (%) (95% CI)
All participants			
Baseline seronegative*	51/1408 (3.62)	96/1362 (7.05)	48.6 (28.4, 63.1)
Mild	11	34	
Moderate	40	57	

Severe	0	5	
Baseline seropositive	12/531 (2.26)	27/544 (4.96)	54.5 (11.1, 77.7)
Regardless of serostatus	63/1939 (3.25)	123/1906 (6.45)	49.7 (32.3, 62.6)
HIV negative participants			
Baseline seronegative	41/1331 (3.08)	89/1289 (6.91)	55.4 (35.9, 68.9)
Baseline seropositive	12/497 (2.42)	26/514 (4.96)	52.3 (6.5, 75.6)
Regardless of serostatus	53/1828 (2.90)	115/1803 (6.38)	54.5 (37.5, 67.0)
HIV positive participants			
Baseline seronegative	10/77 (13.0)	7/73 (9.59)	-35.4 (-236.9, 45.6)
Baseline seropositive	0/34	1/30 (3.33)	
Regardless of serostatus	10/111 (9.01)	8/103 (7.77)	-16.0 (-182.5, 52.4)

*primary endpoint

The results in the complete analysis were similar to those in the initial event driven analysis; VE was 48.6% (95% CI: 28.4, 63.1) in the primary analysis of participants seronegative at baseline. The confidence interval lower bound was again > 0%. The greater number of cases lead to the confidence interval lower bound being close to the WHO threshold of 30%, although the point estimate was still below 50%. If HIV negative participants are considered alone, the WHO criteria are satisfied (VE 54.5%, 95% CI: 37.5, 67.0). It is noted that few HIV positive subjects were enrolled in this trial (5.5%) with only a few symptomatic COVID-19 cases accrued in these subjects.

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

Severe cases and hospitalisations

No cases of severe COVID-19 were reported in NVX-CoV2373 participants compared with 5 cases reported in placebo recipients in the PP-EFF complete analysis set. Five cases in the placebo group required hospitalisation.

IV.5 Clinical safety

Safety population and exposure

Across the 4 clinical trials, a total of 49,950 participants aged 18 years and older received at least one dose of NVX-CoV2373 (n=30,058) at the proposed dose for licensure (5-µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant), or placebo (n=19,892). Over 96% of NVX-CoV2373 and placebo recipients received both doses of NVX-CoV2373/placebo.

Table 16: Number of participants by trial included in the pooled analysis of safety data

Study Number	NVX-CoV2373	Placebo
2019nCoV-101	543	278
2019nCoV-101 - Part 1[1]	29	23
2019nCoV-101 - Part 2[2]	514	255
2019nCoV-501 [3]	2211	2197
2019nCoV-302 [4]	7575[5]	7564[5]
2019nCoV-301	19729	9853
Total	**30058**	**19892**

Abbreviations: HIV = human immunodeficiency virus; NVX-CoV2373 = 5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant; SARS-CoV-2 rS = severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine.

1. Included Groups A (placebo) and C (two-dose regimen of 5 µg SARS-CoV-2 rS with 50 µg Matrix-M Adjuvant) only.
2. Included Groups A (placebo), B (two-dose regimen of 5 µg SARS-CoV-2 rS with 50 µg Matrix-M Adjuvant), and C (5 µg SARS-CoV-2 rS with 50 µg Matrix-M Adjuvant at Dose 1 and placebo at Dose 2) only.
3. Included approximately 240 participants who were HIV-positive in the total population.
4. Included approximately 400 participants who were co-administered seasonal influenza vaccine at Dose 1.
5. These numbers differ from those reported in the 2019nCoV-302 Interim Report (7,569 in the NVX-CoV2373 group and 7,570 in the placebo group) because safety data for 6 participants who received a mixed regimen (placebo at dose 1 and active vaccine at dose 2) were included in the active vaccine group only for the purposes of the pooled analysis of safety data.

The median duration of follow-up in the pooled safety database was 70 days post dose 2. This is shorter than the median follow-up in the individual studies due to censoring at unblinding in the pooled analysis.

Demographic characteristics of subjects in the pooled analysis were generally well balanced between the NVX-CoV2373 and placebo groups.

Table 17: Demographic characteristics of participants in the pooled analysis of safety data

Demographic Characteristics	NVX-CoV2373 N = 30058 n (%)	Placebo N = 19892 n (%)	Total N = 49950
Age			
18 to 64 years	25282 (84.11)	16433 (82.61)	41715
≥ 65 years	4776 (15.89)	3459 (17.39)	8235
Sex			
Male	15826 (52.65)	10364 (52.10)	26190
Female	14232 (47.35)	9528 (47.90)	23760
Race			
White	22415 (74.57)	14808 (74.44)	37223
Black or African American	4417 (14.69)	3256 (16.37)	7673
Asian	1119 (3.72)	691 (3.47)	1810
American Indian or Alaska Native	1322 (4.40)	665 (3.34)	1987
Native Hawaiian or Other Pacific Islander	58 (0.19)	13 (0.07)	71
Multiple	463 (1.54)	260 (1.31)	723
Not Reported	209 (0.70)	134 (0.67)	343
Other	43 (0.14)	54 (0.27)	97
Missing	12 (0.04)	11 (0.06)	23
Ethnicity			
Hispanic/Latino	4463 (14.85)	2262 (11.37)	6725
Not Hispanic/Latino	24647 (82.00)	16747 (84.19)	41394
Not Reported	780 (2.59)	726 (3.65)	1506
Unknown	161 (0.54)	152 (0.76)	313

Local and systemic reactogenicity

Solicited local and systemic adverse events were collected for 7 days after each vaccine dose in studies 101, 301, 501 and a subset of participants in study 302. Grading of solicited adverse events was based on FDA Toxicity Grading Scale for Clinical Abnormalities.

Table 18: Solicited Local Adverse Events for 7 Days Following Each Vaccination Across the SARS-CoV-2 rS Clinical Development Programme

Clinical Trial	2019nCoV-101 (Part 1)[1]		2019nCoV-101 (Part 2)[2]		2019nCoV-501[3]		2019nCoV-302[4]		2019nCoV-301	
Trial Vaccine Group	NVX	Placebo	NVX	Placebo	NVX	Placebo	NVX	Placebo	NVX	Placebo
N1/N2	26/26[5]	23/21	508/250[6]	252/242	2211/2141	2197/2124	1285/1203	1272/1172	18072/17139	8904/8278
Any local TEAE										
Dose 1 (Grade ≥ 1)	18 (69.2)	7 (30.4)	266 (52.4)	39 (15.5)	659 (29.8)	320 (14.6)	762 (59.3)	266 (20.9)	10475 (57.96)	1881 (21.13)
Grade 3	0	0	1 (0.2)	0	32 (1.4)	7 (0.3)	14 (1.1)	2 (0.2)	197 (1.09)	22 (0.25)
Grade 4	0	0	0	0	0	0	0	0	1 (< 0.01)	1 (0.01)
Dose 2 (Grade ≥ 1)	24 (92.3)	4 (19.0)	175 (70.0)	22 (9.1)	616 (28.8)	225 (10.6)	965 (80.2)	199 (17.0)	13525 (78.91)	1797 (21.71)
Grade 3	0	0	13 (5.2)	0	52 (2.4)	9 (0.4)	63 (5.2)	1 (< 0.1)	1140 (6.65)	25 (0.30)
Grade 4	0	0	0	0	0	0	0	0	7 (0.04)	1 (0.01)
Pain										
Dose 1 (Grade ≥ 1)	10 (38.5)	3 (13.0)	139 (27.4)	10 (4.0)	595 (26.9)	261 (11.9)	394 (30.7)	130 (10.2)	6211 (34.37)	986 (11.07)
Grade 3	0	0	0	0	23 (1.0)	4 (0.2)	1 (< 0.1)	1 (< 0.1)	55 (0.30)	3 (0.03)
Grade 4	0	0	0	0	0	0	0	0	0	0
Dose 2 (Grade ≥ 1)	15 (57.7)	2 (9.5)	114 (45.6)	9 (3.7)	570 (26.6)	184 (8.7)	624 (51.9)	107 (9.1)	10227 (59.67)	1141 (13.78)
Grade 3	0	0	5 (2.0)	0	41 (1.9)	8 (0.4)	11 (0.9)	0	297 (1.73)	7 (0.08)
Grade 4	0	0	0	0	0	0	0	0	5 (0.03)	1 (0.01)
Tenderness										
Dose 1 (Grade ≥ 1)	17 (65.4)	7 (30.4)	244 (48.0)	33 (13.1)	360 (16.3)	166 (7.6)	705 (54.9)	223 (17.5)	9450 (52.29)	1494 (16.78)
Grade 3	0	0	1 (0.2)	0	19 (0.9)	2 (< 0.1)	14 (1.1)	1 (< 0.1)	156 (0.86)	18 (0.20)
Grade 4	0	0	0	0	0	0	0	0	1 (< 0.01)	1 (0.01)
Dose 2 (Grade ≥ 1)	21 (80.8)	2 (9.5)	163 (65.2)	18 (7.4)	369 (17.2)	133 (6.3)	922 (76.6)	164 (14.0)	12584 (73.42)	1312 (15.85)
Grade 3	0	0	9 (3.6)	0	31 (1.4)	1 (< 0.1)	49 (4.1)	1 (< 0.1)	834 (4.87)	18 (0.22)
Grade 4	0	0	0	0	0	0	0	0	3 (0.02)	0
Erythema										
Dose 1 (Grade ≥ 1)	0	0	3 (0.6)	0	17 (0.8)	5 (0.2)	25 (1.9)	5 (0.4)	164 (0.91)	27 (0.30)
Grade 3	0	0	0	0	1 (< 0.1)	1 (< 0.1)	0	0	3 (0.02)	0
Grade 4	0	0	0	0	0	0	0	0	0	0
Dose 2 (Grade ≥ 1)	2 (7.7)	1 (4.8)	12 (4.8)	0	34 (1.6)	3 (0.1)	100 (8.3)	2 (0.2)	1138 (6.64)	29 (035)
Grade 3	0	0	3 (1.2)	0	0	0	11 (0.9)	0	143 (0.83)	2 (0.02)
Grade 4	0	0	0	0	0	0	0	0	0	0
Swelling										
Dose 1 (Grade ≥ 1)	0	0	5 (1.0)	1 (0.4)	18 (0.8)	5 (0.2)	12 (0.9)	6 (0.5)	154 (0.85)	24 (0.27)
Grade 3	0	0	0	0	0	1 (< 0.1)	0	0	7 (0.04)	3 (0.03)
Grade 4	0	0	0	0	0	0	0	0	0	0
Dose 2 (Grade ≥ 1)	1 (3.8)	0	14 (5.6)	0	45 (2.1)	4 (0.2)	89 (7.4)	4 (0.3)	1056 (6.16)	25 (0.30)
Grade 3	0	0	1 (0.4)	0	1 (<0.1)	0	5 (0.4)	0	91 (0.53)	2 (0.02)
Grade 4	0	0	0	0	0	0	0	0	0	0

Abbreviations: FDA = United States Food and Drug Administration; N1 = number of participants receiving the first dose of trial vaccine; N2 = number of participants receiving the second dose of trial vaccine; NVX = NVX-CoV2373; NVX-CoV2373 = 5 µg SARS-CoV-2 rS + 50 µg Matrix-M adjuvant; SARS-CoV-2 rS = severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine; TEAE = treatment-emergent adverse events.

1. Group C only.
2. Groups B and C only.
3. Based on Table 14.3.3.1.1.3 of the 2019nCoV-501 Interim Report.
4. Solicited local and systemic TEAEs were evaluated in a subset of 2,714 participants in this study.
5. Excludes 3 sentinel participants who received active vaccine in an open-label manner.
6. Based on Group B only as participants in Group C received placebo for their second vaccination.

Note: Toxicity grading based on FDA toxicity grading scales [DHHS 2007].
Note: Data are presented as number and percentage (n, %) of participants.

Table 19: Solicited Systemic Adverse Events for 7 Days Following Each Vaccination Across the SARS-CoV-2 rS Clinical Development Programme

Clinical Trial	2019nCoV-101 (Part 1)[1]		2019nCoV-101 (Part 2)[2]		2019nCoV-501[3]		2019nCoV-302[4]		2019nCoV-301	
Trial Vaccine Group	**NVX**	**Placebo**	**NVX**	**Placebo**	**NVX**	**Placebo**	**NVX**	**Placebo**	**NVX**	**Placebo**
N1/N2	**26/26[5]**	**23/21**	**510/250[6]**	**251/241**	**2210/2141**	**2196/2123**	**1281/1198**	**1273/1164**	**18072/17139**	**8904/8278**
Any systemic TEAE										
Dose 1 (Grade ≥ 1)	12 (46.2)	9 (39.1)	214 (42.0)	91 (36.3)	632 (28.6)	542 (24.7)	610 (47.6)	482 (37.9)	8614 (47.66)	3562 (40.00)
Grade 3	0	0	13 (2.5)	2 (0.8)	54 (2.4)	46 (2.1)	17 (1.3)	17 (1.3)	422 (2.34)	183 (2.06)
Grade 4	0	0	0	2 (0.8)	0	0	2 (0.2)	0	17 (0.09)	5 (0.06)
Dose 2 (Grade ≥ 1)	17 (65.4)	7 (33.3)	132 (52.8)	66 (27.4)	516 (24.1)	366 (17.2)	774 (64.6)	359 (30.8)	11906 (69.47)	2969 (35.87)
Grade 3	2 (7.7)	1 (4.8)	14 (5.6)	2 (0.8)	71 (3.3)	52 (2.4)	82 (6.8)	16 (1.4)	2056 (12.00)	165 (1.99)
Grade 4	0	0	0	1 (0.4)	0	0	1 (< 0.1)	0	21 (0.12)	5 (0.06)
Nausea or Vomiting										
Dose 1 (Grade ≥ 1)	1 (3.8)	1 (4.3)	25 (4.9)	9 (3.6)	138 (6.2)	109 (5.0)	67 (5.2)	69 (5.4)	1152 (6.37)	488 (5.48)
Grade 3	0	0	1 (0.2)	0	4 (0.2)	7 (0.3)	0	0	17 (0.09)	7 (0.08)
Grade 4	0	0	0	0	0	0	1 (< 0.1)	0	4 (0.02)	3 (0.03)
Dose 2 (Grade ≥ 1)	2 (7.7)	0	18 (7.2)	9 (3.7)	118 (5.5)	81 (3.8)	128 (10.7)	44 (3.8)	1929 (11.26)	450 (5.44)
Grade 3	0	0	0	0	11 (0.5)	6 (0.3)	1 (< 0.1)	0	29 (0.17)	7 (0.08)
Grade 4	0	0	0	0	0	0	0	0	7 (0.04)	2 (0.02)
Headache										
Dose 1 (Grade ≥ 1)	6 (23.1)	7 (30.4)	97 (19.0)	48 (19.1)	384 (17.4)	356 (16.2)	314 (24.5)	274 (21.5)	4505 (24.93)	2028 (22.78)
Grade 3	0	0	1 (0.2)	1 (0.4)	17 (0.8)	20 (0.9)	6 (0.5)	3 (0.2)	146 (0.81)	62 (0.70)
Grade 4	0	0	0	0	0	0	1 (< 0.1)	0	5 (0.03)	1 (0.01)
Dose 2 (Grade ≥ 1)	12 (46.2)	6 (28.6)	74 (29.6)	31 (12.9)	318 (14.9)	232 (10.9)	487 (40.7)	208 (17.9)	7618 (44.45)	1625 (19.63)
Grade 3	0	0	5 (2.0)	1 (0.4)	39 (1.8)	27 (1.3)	17 (1.4)	3 (0.3)	512 (2.99)	36 (0.43)
Grade 4	0	0	0	0	0	0	0	0	6 (0.04)	2 (0.02)
Fatigue										
Dose 1 (Grade ≥ 1)	8 (30.8)	4 (17.4)	121 (23.7)	52 (20.7)	262 (11.9)	199 (9.1)	263 (20.5)	244 (19.2)	4632 (25.63)	1993 (22.38)
Grade 3	0	0	8 (1.6)	1 (0.4)	20 (0.9)	12 (0.5)	6 (0.5)	6 (0.5)	224 (1.24)	100 (1.12)
Grade 4	0	0	0	0	0	0	1 (< 0.1)	0	3 (0.02)	1 (0.01)
Dose 2 (Grade ≥ 1)	12 (46.2)	3 (14.3)	89 (35.6)	33 (13.7)	209 (9.8)	137 (6.5)	491 (41.0)	194 (16.7)	8486 (49.51)	1811 (21.88)
Grade 3	1 (3.8)	1 (4.8)	7 (2.8)	1 (0.4)	19 (0.9)	14 (0.7)	43 (3.6)	9 (0.8)	1419 (8.28)	108 (1.30)
Grade 4	0	0	0	0	0	0	0	0	4 (0.02)	3 (0.04)
Malaise										
Dose 1 (Grade ≥ 1)	3 (11.5)	2 (8.7)	62 (12.2)	30 (12.0)	164 (7.4)	127 (5.8)	149 (11.6)	122 (9.6)	2660 (14.72)	1037 (11.65)
Grade 3	0	0	8 (1.6)	0	10 (0.5)	8 (0.4)	4 (0.3)	4 (0.3)	137 (0.76)	53 (0.60)
Grade 4	0	0	0	1 (0.4)	0	0	1 (< 0.1)	0	7 (0.04)	2 (0.02)
Dose 2 (Grade ≥ 1)	9 (34.6)	3 (14.3)	66 (26.4)	19 (7.9)	148 (6.9)	88 (4.1)	377 (31.5)	107 (9.2)	6674 (38.94)	1018 (12.30)
Grade 3	0	0	6 (2.4)	0	14 (0.7)	10 (0.5)	34 (2.8)	7 (0.6)	1073 (6.26)	57 (0.69)
Grade 4	0	0	0	0	0	0	0	0	9 (0.05)	2 (0.02)
Muscle pain										
Dose 1 (Grade ≥ 1)	6 (23.1)	2 (8.7)	103 (20.2)	27 (10.8)	261 (11.8)	171 (7.8)	286 (22.3)	181 (14.2)	4102 (22.70)	1188 (13.34)
Grade 3	0	0	2 (0.4)	0	20 (0.9)	6 (0.3)	1 (< 0.1)	4 (0.3)	81 (0.45)	35 (0.39)
Grade 4	0	0	0	0	0	0	1 (< 0.1)	0	2 (0.01)	2 (0.02)
Dose 2 (Grade ≥ 1)	12 (46.2)	3 (14.3)	77 (30.8)	16 (6.6)	249 (11.6)	110 (5.2)	492 (41.1)	113 (9.7)	8240 (48.08)	1001 (12.09)
Grade 3	1 (3.8)	0	6 (2.4)	0	22 (1.0)	14 (0.7)	34 (2.8)	3 (0.3)	841 (4.91)	29 (0.35)
Grade 4	0	0	0	0	0	0	0	0	5 (0.03)	4 (0.05)

Clinical Trial	2019nCoV-101 (Part 1)[1]		2019nCoV-101 (Part 2)[2]		2019nCoV-501[3]		2019nCoV-302[4]		2019nCoV-301	
Trial Vaccine Group	**NVX**	**Placebo**	**NVX**	**Placebo**	**NVX**	**Placebo**	**NVX**	**Placebo**	**NVX**	**Placebo**
N1/N2	**26/26[5]**	**23/21**	**510/250[6]**	**251/241**	**2210/2141**	**2196/2123**	**1281/1198**	**1273/1164**	**18072/17139**	**8904/8278**
Joint pain										
Dose 1 (Grade ≥ 1)	1 (3.8)	1 (4.3)	38 (7.5)	15 (6.0)	196 (8.9)	158 (7.2)	84 (6.6)	63 (4.9)	1388 (7.68)	590 (6.63)
Grade 3	0	0	2 (0.4)	0	18 (0.8)	4 (0.2)	0	2 (0.2)	51 (0.28)	29 (0.33)
Grade 4	0	0	0	0	0	0	1 (< 0.1)	0	1 (< 0.01)	0
Dose 2 (Grade ≥ 1)	7 (26.9)	2 (9.5)	37 (14.8)	9 (3.7)	180 (8.4)	109 (5.1)	205 (17.1)	59 (5.1)	3809 (22.22)	567 (6.85)
Grade 3	1 (3.8)	0	3 (1.2)	0	20 (0.9)	8 (0.4)	24 (2.0)	2 (0.2)	411 (2.40)	24 (0.29)
Grade 4	0	0	0	0	0	0	0	0	6 (0.04)	2 (0.02)
Fever										
Dose 1 (Grade ≥ 1)	0	0	12 (2.4)	6 (2.4)	33 (1.5)	32 (1.5)	28 (2.3)	19 (1.5)	66 (0.37)	33 (0.37)
Grade 3	0	0	3 (0.6)	0	5 (0.2)	7 (0.3)	5 (0.4)	2 (0.2)	8 (0.04)	6 (0.07)
Grade 4	0	0	0	1 (0.4)	0	0	1 (< 0.1)	0	6 (0.03)	1 (0.01)
Dose 2 (Grade ≥ 1)	0	0	11 (4.4)	2 (0.8)	48 (2.2)	27 (1.3)	59 (5.1)	9 (0.8)	973 (5.68)	23 (0.28)
Grade 3	0	0	1 (0.4)	0	6 (0.3)	6 (0.3)	7 (0.6)	2 (0.2)	62 (0.36)	3 (0.04)
Grade 4	0	0	0	1 (0.4)	0	0	1 (< 0.1)	0	2 (0.01)	0

Abbreviations: FDA = United States Food and Drug Administration; TEAE = treatment-emergent adverse events; N1 = number of participants receiving the first dose of trial vaccine; N2 = number of participants receiving the second dose of trial vaccine; NVX = NVX-CoV2373; NVX-CoV2373 = 5 µg SARS-CoV-2 rS + 50 µg Matrix-M adjuvant; SARS-CoV-2 rS = severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine.

1. Group C only.
2. Groups B and C only.
3. Based on Table 14.3.3.1.2.3 of the 2019nCoV-501 Interim Report.
4. Solicited local and systemic TEAEs were evaluated in a subset of 2,714 participants in this study.
5. Excludes 3 sentinel participants who received active vaccine in an open-label manner.
6. Based on Group B only as participants in Group C received placebo for their second vaccination.

Note: Toxicity grading based on FDA toxicity grading scales [DHHS 2007].
Note: Data are presented as number and percentage (n, %) of participants.

Overall, there were higher frequencies of solicited adverse events in vaccine recipients compared with those that received placebo. With the exception of study 501, in the vaccine arm the frequency and intensity of events increased after the second vaccine compared with the first.

The majority of participants reported grade 1 or 2 events following each vaccination. In the vaccine arm in studies 301 and 302, grade 3 solicited local events were reported in 1% of participants after the 1st dose and 5% - 7% after the 2nd dose, for systemic events the incidence was 1% - 2% and 7% - 12%. A small number of participants reported grade 4 events.

The most frequent solicited local events following each vaccination were tenderness and pain, and the most frequent solicited systemic events following each vaccination were fatigue, muscle pain, and headache. The frequency and intensity of solicited adverse events was lower in participants ≥65 years of age compared with those aged 18-64 years. The majority of grade 3 and 4 events occurred in the younger age group.

All solicited local and systemic adverse events are considered adverse drug reactions (ADRs). This is reflected in the product information.

An apparent different pattern in reactions was observed in study 501 compared to studies 301 and 302. Lower rates of local and systemic reactions were reported, with no increase after the second dose compared to the first, and reactions were also less often severe. As the reason for this discrepancy between studies is not clear, the rates of reactions reflected in the product information is based on studies 302 and 301 only. The results from studies 301 and 302 are considered sufficiently large and of adequate methodology to characterise the reactogenicity profile.

Unsolicited adverse events

Overall, there were higher frequencies of unsolicited treatment emergent adverse events (TEAEs) within 49 days after first vaccination among NVX-CoV2373 recipients than among placebo recipients. This difference was largely due to reactogenicity events extending beyond the 7-day post-injection window. Unsolicited TEAEs were mostly mild, with severe events occurring in < 1% of participants.

Table 20: Frequencies of unsolicited adverse events reported from after start of first vaccination through 28 days after second vaccination (for example Day 49) in ≥ 0.5% of participants in the pooled analysis of safety data

System Organ Class/Preferred Term (MedDRA Version 23.1)	Participants 18 to ≤ 64 Years		Participants ≥ 65 Years	
	NVX-CoV2373 N = 25282	Placebo N = 16433	NVX-CoV2373 N = 4776	Placebo N = 3459
Any unsolicited TEAE	**4627 (18.30)**	**2577 (15.68)**	**1083 (22.68)**	**639 (18.47)**
General disorders and administration site conditions	**1610 (6.37)**	**544 (3.31)**	**407 (8.52)**	**120 (3.47)**
Fatigue	478 (1.89)	227 (1.38)	115 (2.41)	46 (1.33)
Injection site pain	425 (1.68)	78 (0.47)	145 (3.04)	21 (0.61)
Pyrexia	265 (1.05)	57 (0.35)	34 (0.71)	2 (0.06)
Chills	144 (0.57)	19 (0.12)	22 (0.46)	2 (0.06)
Pain	131 (0.52)	40 (0.24)	22 (0.46)	5 (0.14)
Injection site erythema	78 (0.31)	13 (0.08)	25 (0.52)	2 (0.06)
Injection site pruritus	67 (0.27)	5 (0.03)	28 (0.59)	1 (0.03)
Nervous system disorders	**1042 (4.12)**	**607 (3.69)**	**219 (4.59)**	**126 (3.64)**
Headache	736 (2.91)	390 (2.37)	142 (2.97)	81 (2.34)
Musculoskeletal and connective tissue disorders	**988 (3.91)**	**360 (2.19)**	**286 (5.99)**	**98 (2.83)**
Myalgia	399 (1.58)	102 (0.62)	94 (1.97)	22 (0.64)
Pain in extremity	303 (1.20)	58 (0.35)	107 (2.24)	14 (0.40)
Arthralgia	142 (0.56)	69 (0.42)	30 (0.63)	29 (0.84)
Infections and infestations	**666 (2.63)**	**500 (3.04)**	**143 (2.99)**	**116 (3.35)**
Urinary tract infection	58 (0.23)	43 (0.26)	25 (0.52)	20 (0.58)
Gastrointestinal disorders	**508 (2.01)**	**340 (2.07)**	**108 (2.26)**	**81 (2.34)**
Nausea	156 (0.62)	95 (0.58)	24 (0.50)	23 (0.66)
Diarrhoea	144 (0.57)	123 (0.75)	34 (0.71)	19 (0.55)
Respiratory, thoracic and mediastinal disorders	**494 (1.95)**	**397 (2.42)**	**110 (2.30)**	**65 (1.88)**
Oropharyngeal pain	135 (0.53)	120 (0.73)	29 (0.61)	18 (0.52)
Nasal congestion	127 (0.50)	93 (0.57)	16 (0.34)	16 (0.46)
Cough	118 (0.47)	109 (0.66)	22 (0.46)	11 (0.32)
Rhinorrhoea	91 (0.36)	92 (0.56)	27 (0.57)	18 (0.52)
Skin and subcutaneous tissue disorders	**316 (1.25)**	**165 (1.00)**	**63 (1.32)**	**29 (0.84)**
Injury, poisoning and procedural complications	**249 (0.98)**	**158 (0.96)**	**65 (1.36)**	**43 (1.24)**
Psychiatric disorders	**147 (0.58)**	**80 (0.49)**	**12 (0.25)**	**13 (0.38)**
Vascular disorders	**147 (0.58)**	**87 (0.53)**	**59 (1.24)**	**26 (0.75)**
Hypertension	102 (0.40)	70 (0.43)	46 (0.96)	22 (0.64)
Blood and lymphatic system disorders	**140 (0.55)**	**64 (0.39)**	**17 (0.36)**	**12 (0.35)**
Investigations	**122 (0.48)**	**83 (0.51)**	**32 (0.67)**	**19 (0.55)**
Metabolism and nutrition disorders	**86 (0.34)**	**65 (0.40)**	**26 (0.54)**	**8 (0.23)**
Cardiac disorders	**49 (0.19)**	**27 (0.16)**	**22 (0.46)**	**22 (0.64)**

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment emergent adverse event.
Note: Frequency of TEAEs in each system organ class represents all TEAEs.
Note: Results are presented as n (%) of total number of participants in each treatment group.

Whilst overall there was no imbalance seen in reports of hypertension in the pooled safety data (0.49% in the NVX-CoV2373 group vs 0.46% in the placebo group), an increased incidence of hypertension following NVX-CoV2373 (1.0%) as compared to placebo (0.6%) was observed in older adults during the 3 days following vaccination. 'Hypertension' is included as an adverse event in the product information.

In study 301 there was an imbalance in reports of adverse events related to inflammation of the eye, dysmenorrhoea and menstruation irregular. However, these imbalances were not seen in the other clinical trials and are based on a small number of reports. Adverse events

related to inflammation of the eye and menstrual disorders will be closely followed in the Monthly Safety Summary Reports (MSSRs)/Periodic safety update reports (PSURs).

No events of anaphylaxis have been reported in the clinical trials. There were 8 reports of allergy to vaccine and 3 reports of hypersensitivity in NVX-CoV2373 recipients. None of the three hypersensitivity events are considered related to NVX-CoV237. Upon review of the narratives of the 8 reports of 'allergy to the vaccine', these were mostly reactogenicity related events rather than clear hypersensitivity reactions to the vaccine. There was one case which may concern true hypersensitivity, namely an erythematous patch on the hand and itchiness as mild in intensity with onset 10 minutes after vaccination, which was resolved within 3 hours.

Serious adverse events

The number of deaths reported across the studies was very low and balanced between the vaccine and placebo groups. None of the deaths were considered related to study vaccine.

Overall, the incidence of serious adverse events (SAEs) was low and balanced between the vaccine and placebo groups.

Numerical imbalances in SAEs of cholecystitis (9 vs 0) and Cerebrovascular accident (7 vs 1) were seen in study 301. Similar imbalances were not seen in the other clinical studies, all participants had at least one underlying risk factor and there was no consistent pattern in the time from last vaccine dose to onset of symptoms. These events will be kept under review in MSSRs/PSURs.

A numerical imbalance was also seen in SAEs of prostate cancer (5 vs 0) in study 301 only. Considering the short latency between the diagnoses of prostate cancer, the presence of underlying risk factors, the absence of biological plausibility and the number of cases observed being within the expected cases based on background rates, the events of prostate cancer are considered unlikely related to NVX-CoV2373.

There were 3 SAEs of myocarditis reported: 2 in the vaccine group and one in the placebo group. Three additional cases of myocarditis/pericarditis were identified post vaccine cross over. A possible alternative aetiology was identified in all 5 cases reported in the vaccine group. However, as myocarditis and pericarditis are known adverse events for some of the approved COVID-19 vaccines (mRNA vaccines) and because a possible causal role of vaccination could not be excluded in 3 cases due to the time to onset from last vaccination, 'Myocarditis/Pericarditis' is included in the RMP as an 'Important potential risk'.

Table 21: Serious Adverse Events Reported from After Start of First Vaccination Through the Respective Data Cut-off Dates of the Individual Clinical Trials with an Incidence Rate > 0.05 e/100 PY in the Pooled Analysis of Safety Data

System Organ Class/ Preferred Term (MedDRA Version 23.1)	NVX-CoV2373 N = 30058	Placebo N = 19892
Total follow-up time (person-year)	**7465.0**	**4877.1**
Median follow-up time after first vaccination (days)	**92**	**91**
Any SAE	**284 (3.80)**	**197 (4.04)**
Infections and infestations	**46 (0.62)**	**55 (1.13)**
COVID-19	8 (0.11)	11 (0.23)
Appendicitis	7 (0.09)	7 (0.14)
Pneumonia	4 (0.05)	5 (0.10)
COVID-19 pneumonia	1 (0.01)	12 (0.25)
Diverticulitis	0	3 (0.06)
Injury, poisoning and procedural complications	**40 (0.54)**	**21 (0.43)**
Fall	1 (0.01)	3 (0.06)
Overdose	1 (0.01)	3 (0.06)
Cardiac disorders	**35 (0.47)**	**19 (0.39)**
Atrial fibrillation	7 (0.09)	3 (0.06)
Cardiac arrest	3 (0.04)	3 (0.06)
Nervous system disorders	**23 (0.31)**	**14 (0.29)**
Cerebrovascular accident	7 (0.09)	1 (0.02)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**19 (0.25)**	**11 (0.23)**
Prostate cancer	5 (0.07)[1]	0
Gastrointestinal disorders	**19 (0.25)**	**10 (0.21)**
Respiratory, thoracic and mediastinal disorders	**17 (0.23)**	**11 (0.23)**
Pulmonary embolism	4 (0.05)	3 (0.06)
Psychiatric disorders	**12 (0.16)**	**10 (0.21)**
Suicidal ideation	3 (0.04)	3 (0.06)
Vascular disorder	**12 (0.16)**	**6 (0.12)**
Hepatobiliary disorders	**12 (0.16)**	**1 (0.02)**
Cholecystitis acute	5 (0.07)	0
General disorders and administration site conditions	**8 (0.11)**	**6 (0.12)**
Chest pain	1 (0.01)	3 (0.06)
Renal and urinary disorders	**6 (0.08)**	**8 (0.16)**
Nephrolithiasis	1 (0.01)	3 (0.06)
Musculoskeletal and connective tissue disorders	**6 (0.08)**	**3 (0.06)**
Pregnancy, puerperium and perinatal conditions	**6 (0.08)**	**2 (0.04)**
Blood and lymphatic system disorders	**5 (0.07)**	**4 (0.08)**
Metabolism and nutrition disorders	**4 (0.05)**	**9 (0.18)**
Investigations	**0**	**3 (0.06)**

Abbreviations: e/100 PY = events per 100 person-years; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event; NVX-CoV2373 = 5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant; SARS-CoV-2 rS = severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine.
1. One event of prostate cancer was censored from the pooled analysis of safety data because the event occurred after the unblinding date (this event was included in the 2019nCoV-301 Interim Report).
Note: Results are presented as number of events per 100 person-years, with the event rate in parentheses.

Adverse events of special interest

Adverse events of special interest included potential immune-mediated medical conditions (PIMMCs) as well as adverse events related to COVID-19.

No imbalances in AESI were seen in studies 302, 501 or 101. However, in study 301 an apparent higher incidence of PIMMCs was reported in the NVX-CoV2373 group compared with placebo. The type of events reported are diverse, with no clear patterns emerging aside

from the overall imbalance. Furthermore, whilst exploring this signal, the applicant conducted a MedDRA SMQ which identified additional events in both treatment groups not reported by investigators and therefore not included in the original analysis. This updated analysis did not suggest an imbalance.

Laboratory findings

Clinical laboratory findings were only reported for study 2019nCoV-101 (Part 1), where haematology and serum chemistry formed part of the safety assessments. No concerns are raised from this data.

Across the clinical studies there were similar rates of laboratory investigation TEAEs for NVX-CoV2373 compared with placebo.

Safety in special populations

Pregnancy and breastfeeding

Women who were pregnant or breastfeeding were excluded from the clinical trials.

As such, there is limited experience with NVX-CoV2373 in pregnancy. Up to 26 October 2021, 137 pregnancies have been reported of which 95 received NVX-CoV2373 and 42 received placebo. Of the 95 pregnancies reported in participants in the NVX-CoV2373 group, 8 resulted in live births, 11 underwent voluntary termination, 16 resulted in spontaneous abortion, and 60 were either ongoing (55) or the outcome of the pregnancy was unknown (5). There were no foetal deaths or stillbirths reported in the clinical development program.

There are no data available on the safety of NVX-CoV2373 administered during breastfeeding.

'Use in pregnancy and whilst breastfeeding' is proposed for inclusion in the RMP as 'Missing information'. Planned additional pharmacovigilance activities include a Pregnancy and Infant Outcomes Safety Study using the "COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER)

Paediatric population

The proposed indication is in subjects aged 18 years and over. No data was provided in this submission for subjects less than 18 years of age. A national paediatric investigation plan has been agreed and a deferral granted: MHRA-100149-PIP01-21.

Immunosuppression

Participants with any confirmed or suspected immunosuppressive or immunodeficient state were excluded from the clinical trials. 'Use in immunocompromised patients' is included as 'Missing information' in the RMP with a number of additional pharmacovigilance activities planned to address this.

In study 501 the safety of NVX-CoV2373 was evaluated in 244 HIV positive participants aged 18 to ≤ 64 years of age (122 in each treatment group). These participants were required to be medically stable (including having been completely free of opportunistic infection in

the 1 year prior to the first study vaccination), receiving highly active antiretroviral therapy (and been using the same regimen within at least 8 weeks before screening), and have a HIV-1 viral load < 1000 copies/mL within 45 days of randomization. In this small subset of medically stable HIV positive participants, there was no clear pattern of a differential safety profile of NVX-CoV2373 by HIV status.

SARS-CoV-2 serostatus at baseline

Available data does not suggest that baseline serostatus impacts the reactogenicity (frequency of solicited AEs) or safety of NVX-CoV2373 with very similar rates of treatment emergent solicited and unsolicited AEs reported in both participants seropositive as well as seronegative at baseline.

Safety related to interactions

An exploratory licensed seasonal influenza co-administration sub-study was conducted as part of study 302. Licensed inactivated seasonal influenza vaccines were co-administered to participants on the same day as Dose 1 of NVX-CoV2373 (n = 217) or placebo (n = 214) in the opposite deltoid muscle of the arm. The frequency of solicited local and systemic adverse reactions in the influenza sub-study population was higher than that in the main study population following Dose 1 in both NVX-CoV2373 and placebo recipients. However, the intensity of events was similar with the majority of subjects in the vaccine arm reporting grade 1 events following their first dose. The incidence of grade 3 events remained low and similar between those included/not included in the influenza substudy.

Discontinuations due to adverse events

There were few discontinuations (vaccination/study) due to treatment emergent adverse events. Overall, there were slightly more discontinuations in the vaccine group compared with placebo, this was largely due to reactogenicity events e.g. headache, injection-site pain, myalgia.

IV.6 Risk Management Plan (RMP)

The applicant has submitted a~~n~~ RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects

Clinical immunogenicity

The immune response data in the interim reports support the choice of a two-dose schedule of Nuvaxovid, with no apparent advantage for 25 over 5 µg antigen doses in the adjuvanted formulations.

The final clinical study reports from studies 2019nCoV-101 part 1 and 2, 2019nCoV-301, 2019nCoV-302 and 2019nCoV-501 should be submitted as soon as these are available. This is captured in the RMP.

Three clinical immunogenicity recommendations are made: the applicant should i) investigate the need of a booster dose, ii) detail their plans to establish an immunologic correlate of protection, and iii) investigate (with regular updates) the ability of the vaccine to neutralise emerging SARS-CoV-2 variants.

Clinical efficacy

Robust and high protective short-term efficacy against COVID-19 has been demonstrated in individuals aged 18 years and older in two pivotal observer blinded placebo controlled trials. The vaccine is efficacious across different high-risk groups including older adults, as well as subjects considered at increased risk of severe disease due to underlying chronic disease. Whilst lower vaccine efficacy was observed in a supportive trial 2019nCoV-501 in South Africa, this was possibly due to reduced efficacy against the Beta variant circulating at that time.

Clinical safety

Overall, the short-term safety profile of Nuvaxovid in individuals aged 18 years and older is adequately characterised and appears acceptable. The safety population, exposure and duration of follow-up are considered acceptable in the context of a conditional marketing authorisation application for a COVID-19 vaccine. Safety data corresponding to longer follow-up will be submitted as laid out in the Risk Management Plan.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the application in accordance with legal requirements.

The PIL has been evaluated via a user consultation study in accordance with legal requirements. The results show that the PIL meets the criteria for readability as set out in the guideline on the readability of the label and package leaflet of medicinal products for human use.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable. The non-clinical and clinical data submitted have shown the positive benefit/risk of this product for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

Nuvaxovid has been authorised with a Conditional Marketing Authorisation (CMA). The Marketing Authorisation Holder shall complete, within the stated timeframe, the following measures:

SPECIFIC OBLIGATIONS

Description	Due date
In order to ensure consistent product quality during shelf life, the MAH should provide additional information on stability of the finished product.	31 January 2023
In order to ensure consistent quality over the product life cycle, the MAH should adequately bridge the reference standards and review the finished product potency limits when additional data become available.	31 July 2022

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, and in line with current guidelines.

In accordance with legal requirements, the current approved UK/GB/NI versions of the SmPCs and PILs for these products are available on the MHRA website.

Representative copies of the labels at the time of licensing have been provided.

TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**