EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

04 January 2022
EMA/783213/2021
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Nuvaxovid

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

Procedure No. EMEA/H/C/005808/0000

Note

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

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Table of contents

List of abbreviations

2P	Proline amino acid substitutions inserted at positions K986P and V987P within the heptad repeat 1 domain
3Q	Mutation of the putative furin cleavage site RRAR to QQAQ located within the S1/S2 cleavage domain
Ab	Antibody
ACB	Accession Cell Bank
ACE2	Angiotensin-converting enzyme 2
ADME	Absorption, distribution, metabolism, and excretion
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AEX	Anion Exchange Chromatography
AF4-MALS	Asymmetrical-Flow Field-Flow Fractionation with MALS detection
anti-S IgG	Anti-spike immunoglobulin G
APC	Antigen presenting cell
AR	Assessment report
ARDS	Acute respiratory distress syndrome
ATC	Anatomical Therapeutic Chemical
ATCC	American Type Culture Collection
BAL	Bronchoalveolar lavage
BALB/c	Bagg and Albino immunodeficient mice
BLI	Biolayer Interferometry
BMI	Body mass index
BSE	Bovine Spongiform Encephalopathy
BV	Baculovirus
BVI	Baculovirus inoculum
BWP	EMA Biologics Working Party
CD	Cluster of differentiation
CDC	US Centers for Disease Control and Prevention
CEPI	Coalition for Epidemic Preparedness Innovations
CH	Cholesterol
CHMP	Committee for Medicinal Products for Human use
CHO	Chinese hamster ovary
CI	Confidence interval
cMA	Conditional Marketing Authorisation
cMAA	Conditional Marketing Authorisation Application
CMI	Cell-mediated immune(ity)
CoA	Certificate of Analysis
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CPE	Cytopathic Effect
CPP	Critical process parameter
CPRD	UK Clinical Practice Research Datalink database
CQA	Critical Quality Attribute
CRP	C-reactive protein
CSR	Clinical Study Report
CVA	Cerebrovascular accident
DART	Developmental and Reproductive Toxicology

DL	Detection limit
DLS	Dynamic light scattering
DOE	Design of experiments
DP	Drug product
DS	Drug substance
DSC	Differential Scanning Calorimetry
DSMB	Data safety monitoring board
DV	Diafiltration Volume
E	Envelope
EBD	European birth date
EBOV GP	Ebolavirus glycoprotein
EBSI	Emergent BioSolutions, Inc
EC	European Commission
ECDC	European Centre for Disease Prevention and Control
eDiary	Electronic diary
EEA	European Economic Area
EHR	Electronic Health Record
ELISA	Enzyme-linked immunosorbent assay
ELISpot	Enzyme-linked immunosorbent spot
EMA	European Medicines Agency
EMBASE	Excerpta Medica dataBASE
EN	English
EOPCB	End-of-Production Cell Bank
EoS	End of study
EOT	End of treatment
eRMR	EVDAS Electronic Monitoring
ETF	COVID-19 EMA pandemic Task Force
EU	European Union
EURD	European reference date
FAS	Full Analysis Set
FBS	Foetal Bovine Serum
FDA	US Food and Drug Administration
FDBK	FujiFilm Diosynth United Kingdom
FDBU	Fujifilm Diosynth Biotechnologies United States
FFT	Flexible freeze thaw
FTM	Fluid Thioglycollate Medium
GAVI	Global Alliance for Vaccines and Immunizations
GC	Germinal centre
GCP	Good Clinical Practice
GD	Gestational Day
GLP	Good Laboratory Practice
GMEU	Geometric mean ELISA unit(s)
GMP	Good Manufacturing Practice
GMT	Geometric mean titer(s)
hACE2	Human angiotensin-converting enzyme 2
HCP	Host-cell protein
HIV	Human immunodeficiency virus
HLT	High Level Term
HPSEC-MALS	High Performance Size-Exclusion Chromatography coupled with Multi-Angle Light Scattering detection

HR1	Heptad repeat 1 (domain)
HVP	Host-virus Protein
IBD	International birth date
ICCS	Intracellular cytokine staining
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICSR	Individual Case Safety Report
ICU	Intensive care unit
IFN-γ	Interferon gamma
IgG	Immunoglobulin G
IL-2	Interleukin 2
IL-4	Interleukin 4
IM	Intramuscular(ly)
IPC	In-process Control
IRB	Institutional review board
ISCOM	Immune Stimulating Complex(es)
ISO	International Organization for Standardization
ITT	Intent-to-treat
KPA	Key Product Attribute
KPP	Key Process Parameter
LBCI	Lower bound confidence interval
LC-MS	Liquid chromatography-mass spectrometry
LER	Low Endotoxin Recovery
LTCF	Long-term care facilities
M	Membrane
MA	Marketing authorisation
MAA	Marketing authorisation application
MCB	Master cell bank
MCWB	Master Working Cell Bank
MedDRA	Medical Dictionary for Regulatory Activities
MERS-CoV	Middle East respiratory syndrome coronavirus
MHRA	Medicines and Healthcare products Regulatory Agency
MHC	Major histocompatibility complex
MN	Microneutralisation
MOI	Multiplicity Of Infection
MPS	Massive Parallel Sequencing
MS	Mass Spectrometry
MSs	Member states
MSSR	Monthly summary safety report
MVS	Master Virus Stock
N	Number
N	Nucleocapsid
nAb	Neutralising antibody(ies)
NAS	New active substance
NGS	Next generation sequencing
NHP	Non-human primate
NIV	Nanoparticle Influenza Vaccine
NKPP	Non-key Process Parameter
NLS	Noble Life Sciences

NOEC	No observed effect concentration
NOR	Normal operating range
NTA	Nanoparticle Tracking Analysis
O/E	Observed versus expected
OECD	Organisation for Economic Co-operation and Development
OFAT	One-factor-at-a-time
OUHSC	Oklahoma University Health Sciences Centre
PACMP	Post-Approval Change Management Protocol
PAD	Pulsed Amperometric Detection
PBMC	Peripheral blood mononuclear cell(s)
PBRT	PCR Based Reverse Transcriptase
PBS	Phosphate-buffered saline
PC	Phosphatidylcholine
PCR	Polymerase chain reaction
PCS	Process Control Strategy
PDCO	Paediatric Committee
PEC	Predicted environmental concentration
PEC	Positive extraction control
PERT	Product Enhanced Reverse Transcriptase
PETG	Polyethylene Terephthalate Glycol
Ph. Eur.	*European Pharmacopoeia*
PhV	Pharmacovigilance
PI	Product information
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic(s)
PL	Package Leaflet
PLWH	People living with HIV
PND	Post-natal day
PP	Process parameter
PP-EFF	Per-protocol efficacy
PPQ	Process Performance Qualification
PRAC	Pharmacovigilance Risk Assessment Committee
PS80	Polysorbate 80
PSUR	Periodic safety update report
PT	Preferred term
PVS	Pre-Master Virus Stock
PvSS	Pharmacovigilance Signaling System
PY	Patient year(s)
QA	Quality attribute
QbD	Quality by Design
QR	Quick response
R	Recombinant
RBD	Receptor-binding domain
REC	CHMP recommendation, EMA Post-Authorisation Measure (PAM)
RMP	Risk management plan
RNA	Ribonucleic acid
rS	Recombinant Spike protein
RSV-F	Respiratory syncytial virus fusion (protein)
RT	Reverse transcriptase
RT-PCR	Reverse transcription polymerase chain reaction

S	Spike (protein)
SA	Saponin
SAE	Serious adverse event
SARS	Severe acute respiratory syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SARS-CoV-2 rS	SARS-CoV-2 recombinant spike protein nanoparticle vaccine
SCDM	Soybean Casein Digest Medium
SCR	Seroconversion rate
SDS-PAGE	Sodium dodecyl sulfate polyacrylamide gel electrophoresis
Sf9	Spodoptera frugiperda 9
SFM	Serum-free medium
sgRNA	Subgenomic ribonucleic acid
SIIPL	Serum Institute of India Pvt tLtd.
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOB	CHMP specific obligation, EMA Post-Authorisation Measure (PAM)
SOC	System organ class
ssRNA	Single-stranded RNA
SVA	Statens veterinärmedicinska anstalt, Swedish National Veterinary Institute
TEAE	Treatment-emergent adverse event
TEM	Transmission Electron Microscopy
TFF	Tangential Flow Filtration
Tfh	T follicular helper
TGA	Therapeutic Goods Administration, Australia
Th1	T-helper 1
Th2	T-helper 2
TMP	Transmembrane Pressure
TNF-α	Tumour necrosis factor alpha
TSE	Transmissible Spongiform Encephalopathy
TTO	Time to onset
ULDPE	Ultra-low Density Polyethylene
UMSOM	University of Maryland School of Medicine
UK	United Kingdom
URL	Uniform Resource Locator
US	United States of America
USP	United States Pharmacopoeia
USP/NF	United States Pharmacopoeia/National Formulary
UVCD	UV circular dichroism
VAED	Vaccine-induced enhancement of disease
VAERD	Vaccine-associated enhanced respiratory disease
VAERS	Vaccine Adverse Event Reporting System
VE	Vaccine efficacy
VOC	Variant(s) of concern
VOI	Variant(s) of interest
WBC	White blood cell count
WCB	Working cell bank
WHO	World Health Organisation
wt	Wild type
WVB	Working Virus Bank
WVS	Working Virus Stock

yoa	Years of age
ZIKV EnvD	Zika virus envelope dimers

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Novavax CZ, a.s. submitted on 16 November 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Nuvaxovid, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 6 November 2020.

The applicant applied for the following indication: Nuvaxovid is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0126/2021 on the agreement of a paediatric investigation plan (PIP).

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

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

1.5. Applicant's requests for consideration

1.5.1. Conditional marketing authorisation

The applicant requested consideration of its application for a Conditional marketing authorisation in accordance with Article 14-a of the above-mentioned Regulation. as it is intended for the prophylaxis of a life-threatening disease. In addition, the above-mentioned medicinal product is intended for use in an emergency situation, in response to public health threats duly recognised by the World Health Organisation and by the Union.

1.5.2. New active Substance status

The applicant requested the active substance SARS-CoV-2 recombinant spike protein contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Scientific advice

The applicant received the following Scientific Advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
12 October 2020	EMEA/H/SA/4686/1/2020/III	Prof Brigitte Schwarzer-Daum, Dr Mair Powell

The Scientific Advice pertained to the following quality/non-clinical/clinical aspects:

- Comparability exercise to assess production of active substance, Matrix-M1 adjuvant and finished product at additional manufacturing facilities
- Lot release testing protocol for active substance and finished product
- Non-clinical development plan
- Clinical data package to support a conditional MAA
- Advice on paediatric vaccine development and timelines

Compliance with Scientific Advice

Clinical aspects discussed included the acceptability of the proposed clinical development programme to support a potential (c)MA proposing study 2019nCoV-501 as pivotal study, as well as the acceptability of the target of demonstrating a VE of 50% with a lower bound of the 95% CI of >0. This was not accepted as sufficient, indicating the lower bound of the CI should at least be ≥20% and preferably ≥30%. Considering the submission is no longer in line with the proposal in the advice (i.e., 2019nCoV-501 is not the pivotal study), the following comments were provided in this advice on the clinical development plan which hold relevance:

- The safety and immunogenicity data obtained in Part 1 support inclusion of the adjuvant and administration of a second dose, with no apparent advantage for 25 vs. 5 µg antigen doses in the adjuvanted formulations.
- It was advised that the study would have a single primary efficacy endpoint based on prevention of COVID-19 disease of any severity. This was followed.
- There was concern regarding the definitions for severity of disease. More stringent categorisation was recommended. This has not been followed.
- It was found acceptable that the primary analysis is conducted in baseline seronegative subjects and counting cases from day 7 after the second dose. However, it was recommended that only these criteria would be applied as exclusions for the primary analysis population. Analyses of the primary endpoint in other sub-populations should be designated as secondary. Sensitivity analyses should be planned counting all cases from randomisation, all cases after dose 1 and all cases after dose 2, each of which should be conducted in baseline seronegatives and in the total study population. These analyses have only in part been provided.

- Given the nature of this vaccine, it was found acceptable that solicited local and systemic reactogenicity data were collected for 7 days after both doses.

1.7. COVID-19 EMA pandemic Task Force (COVID-ETF)

In line with their mandate as per the EMA Emerging Health Threats Plan, the ETF undertook the following activities in the context of this marketing authorisation application:

The ETF endorsed the Scientific Advice letter, confirmed eligibility to the rolling review procedure based on the information provided by the applicant and agreed the start of the rolling review procedure.

Furthermore, the ETF discussed the (Co-)Rapporteur's assessment reports overviews and provided their recommendation to the CHMP in preparation of the written adoption rolling review procedures. The corresponding interim opinions were subsequently adopted by the CHMP.

For the exact steps taken at ETF, please refer to section 1.8.

1.8. Steps taken for the assessment of the product

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

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

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Brigitte Keller-Stanislawski

ETF discussion on Scientific Advice EMEA/H/SA/4686/1/0000/III on	8 October 2020
The CHMP confirmed eligibility to the centralised procedure on	26 October 2020
ETF recommendation on a request for appointment of Rapporteurs for a potential rolling review procedure on	12 November 2020
Agreement by ETF to start the rolling review procedure on	2 February 2021
The applicant submitted documentation as part of a rolling review on non-clinical data to support the marketing authorisation application on	2 February 2021
The procedure (Rolling Review 1) started on	3 February 2021
The Rapporteur's first Assessment Report was circulated to all CHMP, Peer Reviewer and ETF on	4 March 2021
The Co-Rapporteur's first Assessment Report was circulated to all CHMP, Peer Reviewer and ETF on	4 March 2021
The Rapporteurs circulated updated Joint Assessment reports to all CHMP, Peer Reviewer and ETF on	17 March 2021
ETF discussions took place on	19 March 2021
Adoption of first Interim Opinion on the RR for this rolling review on	23 March 2021
The applicant submitted documentation as part of a rolling review on non-clinical data to support the marketing authorisation application on	20 April 2021

The procedure (Rolling Review 2) started on	21 April 2021
The Rapporteur's first Assessment Report was circulated to all CHMP, Peer Reviewer and ETF on	27 May 2021
The Co-Rapporteur's first Assessment Report was circulated to all CHMP, Peer Reviewer and ETF on	27 May 2021
Updated joint draft overview and LoQ drafted by Rapporteurs and circulated to CHMP and ETF on	4 June 2021
ETF discussions took place on	8 June 2021
Adoption of the 2nd interim opinion for this rolling review on	11 June 2021
The following GMP and GCP inspections were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GMP inspection at the active substance manufacturing and quality control site in South Korea on 22 March 2021. The outcome of the inspection carried out was issued on	22 April 2021
– A PhV pre-authorisation inspection at a CRO in Belgium between 30 August and 2 September 2021. The outcome of the inspection carried out was issued on	29 October 2021
The applicant submitted documentation as part of a rolling review on clinical data to support the marketing authorisation application on	22 March 2021; 21 May 2021, 8 June 2021 and 31 August 2021
The procedure (Rolling Review 3) started on	1 September 2021
The Rapporteur's first Assessment Report was circulated to all CHMP, Peer Reviewer and ETF on	20 October 2021
The Co-Rapporteur's first Assessment Report was circulated to all CHMP, Peer Reviewer and ETF on	20 October 2021
PRAC Rapporteur's first Assessment Report was circulated to all CHMP, Peer Reviewer and ETF on	20 October 2021
PRAC Rapporteur's updated Assessment Report was circulated to all CHMP, Peer Reviewer and ETF on	28 October 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during an extraordinary meeting on	28 October 2021
Updated joint draft overview and LoQ drafted by Rapporteurs and circulated to CHMP and ETF on	2 November 2021
ETF discussions took place on	4 November 2021
The CHMP endorsed the 3rd interim opinion for this rolling review on	8 November 2021
The applicant submitted documentation as part of a rolling review on quality to support the marketing authorisation application on	10 September 2021 and 29 October 2021

The procedure (Rolling Review 4) started on	3 November 2021
Preliminary List of Questions from Rapporteurs received on	11 November 2021
The applicant submitted responses to List of Questions on	23-25 November 2021
The Rapporteur's first Assessment Report was circulated to all CHMP, Peer Reviewer and ETF on	30 November 2021
The Co-Rapporteur's first Assessment Report was circulated to all CHMP, Peer Reviewer, BWP and ETF on	30 November 2021
BWP meetings were held on	26 November 2021 and 6 December 2021
Joint LoQ following BWP sent on	6 December 2021
The applicant submitted responses to List of Questions on	8 December 2021
The Rapporteur's joint Assessment Report was circulated to all CHMP, Peer Reviewer, BWP and ETF on	10 December 2021
A BWP meeting was held on	15 December 2021
The application for the marketing authorisation was formally received by the EMA on	16 November 2021
The procedure started on	17 November 2021
The Rapporteur's first Assessment Report was circulated to all CHMP, BWP, peer reviewer and ETF on	29 November 2021
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	29 November 2021
CHMP Rapporteurs circulated the Joint Assessment Report to all CHMP, PRAC, ETF and EMA on	3 December 2021; 9 December 2021 and 14 December 2021
ETF discussions took place on	9 December 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during an extraordinary meeting on	13 December 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Nuvaxovid during an extraordinary meeting on	20 December 2021
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS) on	20 December 2021
A revised opinion was adopted by the CHMP to implement a temporary exemption to Article 51 of Directive 2001/83/EC for QC testing for batch release to be conducted in the EEA, until 31st March 2022	04 January 2022

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

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

2.1.2. Epidemiology and risk factors

As of 1st March 2021, there have been over 113 million confirmed cases of SARS-CoV-2 infection globally with approximately 2.5 million deaths resulting from infection and subsequent coronavirus disease (COVID-19). The majority of infections result in asymptomatic or mild disease with full recovery. Underlying health conditions such as hypertension, diabetes, cardiovascular disease, chronic respiratory disease, chronic kidney disease, immune compromised status, cancer and obesity are considered risk factors for developing severe COVID-19. Other risk factors include organ transplantation and chromosomal abnormalities. Increasing age is another risk factor for severe disease and death due to COVID-19. European countries that have established surveillance systems in long-term care facilities (LTCF) have reported that 5-6% of all current LTCF residents died of COVID-19, and that LTCF residents accounted for up to 72% of all COVID-19 related deaths. Individuals with high risk of exposure to SARS-CoV-2 due to occupation include healthcare and frontline workers.

2.1.3. Aetiology and pathogenesis

SARS-CoV-2 is a positive-sense single-stranded RNA (+ssRNA) virus, with a single linear RNA segment. It is enveloped and the virions are 50–200 nanometres in diameter. Like other coronaviruses, SARS-CoV-2 has four structural proteins, known as the S (spike), E (envelope), M (membrane), and N (nucleocapsid) proteins. The spike protein contains a polybasic cleavage site, a characteristic known to increase pathogenicity and transmissibility in other viruses. The Spike is responsible for allowing the virus to attach to and fuse with the membrane of a host cell. The S1 subunit catalyses attachment to the angiotensin-converting enzyme 2 (ACE2) receptor present on cells of the respiratory tract, while the S2 subunit facilitates fusion with the cell membrane. The spike protein is considered a relevant antigen for vaccine development because it was shown that antibodies directed against it neutralise the virus and it elicits an immune response that prevents infection in animals.

It is believed that SARS-CoV-2 has zoonotic origins and it has close genetic similarity to bat coronaviruses. Its gene sequence was published mid-January 2020 and the virus belongs to the betacoronaviruses. Human-to-human transmission of SARS-CoV-2 was confirmed in January 2020.

Transmission occurs primarily via respiratory droplets from coughs and sneezes and through aerosols. The median incubation period after infection to the development of symptoms is four to five days. Most symptomatic individuals experience symptoms within two to seven days after exposure, and almost all symptomatic individuals will experience one or more symptoms before day twelve. Common symptoms include fever, cough, fatigue, breathing difficulties, and loss of smell and taste and symptoms may change over time.

The major complication of severe COVID-19 is acute respiratory distress syndrome (ARDS) presenting with dyspnoea and acute respiratory failure that requires mechanical ventilation. In addition to respiratory sequelae, severe COVID-19 has been linked to cardiovascular sequelae, such as myocardial injury, arrhythmias, cardiomyopathy and heart failure, acute kidney injury often requiring renal replacement therapy, neurological complications such as encephalopathy, and acute ischemic stroke.

2.1.4. Clinical presentation and diagnosis

The severity of COVID-19 varies. The disease may take a mild course with few or no symptoms, resembling other common upper respiratory diseases such as the common cold. Mild cases typically recover within two weeks, while those with severe or critical diseases may take three to six weeks to recover. Among those who have died, the time from symptom onset to death has ranged from two to eight weeks. Prolonged prothrombin time and elevated C-reactive protein levels on admission to the hospital are associated with severe course of COVID-19 and with a transfer to ICU. The gold standard method of testing for presence of SARS-CoV-2 is the reverse transcription polymerase chain reaction (RT-PCR), which detects the presence of viral RNA fragments. As this test detects RNA but not infectious virus, its ability to determine duration of infectivity of patients is limited. The test is typically done on respiratory samples obtained by a nasopharyngeal swab, a nasal swab or sputum sample.

2.1.5. Management

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

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

2.2. About the product

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

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

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

Nuvaxovid is administered intramuscularly as a course of 2 doses of 0.5 mL each. It is recommended to administer the second dose 3 weeks after the first dose.

The intended indication for Nuvaxovid is 'for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older'.

2.3. Type of Application and aspects on development

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of the above-mentioned Regulation, based on the following criteria:

- The benefit-risk balance is positive.

According to the applicant, the benefit-risk balance of Nuvaxovid is positive in the active immunisation to prevent COVID-19 disease caused by SARS-CoV-2 virus, in individuals 18 years of age and older. To demonstrate positive benefit-risk balance for this product, the applicant submitted data from non-clinical and clinical studies as well as supportive literature references.

The applicant considers that the non-clinical program has demonstrated that Nuvaxovid generates a robust and functional immune response, eliciting neutralising antibodies against SARS-CoV-2, resulting in protective efficacy following live viral challenge across multiple species. No adverse risks have been identified in the non-clinical testing program and the data support the proposed dose and regimen for human use.

The applicant provided results from two pivotal Phase 3 studies, showing that Nuvaxovid prevents PCR-confirmed symptomatic mild, moderate, or severe COVID-19 with observed efficacies of ~90%, with comparable efficacies against non-B.1.1.7 variant strains (96.4%) and variants that were either considered of concern or interest (VOC/VOI) (93.2%) or not considered VOC/VOI (100%) and specifically against the B.1.1.7 (Alpha) variant (86.3% and 93.6%, in each of the two pivotal studies, respectively). Among Nuvaxovid recipients, there have been no cases of severe disease with an onset from at least 7 days after second vaccination, which mitigates concerns over vaccine-enhanced respiratory disease. The clinical benefit was consistent across all participants. Based on the administration of Nuvaxovid to 30,058 adults, there have been no safety concerns and the safety profile has been largely characterised by mild or moderate reactogenicity reactions of short duration.

Based on the totality of the data across the SARS-CoV-2 rS clinical development program, the applicant therefore considers that Nuvaxovid is an effective vaccine with an acceptable safety profile, and that the known and potential benefits of the product outweigh its known and potential risks.

- It is likely that the applicant will be able to provide comprehensive data.

The applicant has provided consolidated quality, non-clinical and clinical data packages for review under the rolling review procedure. For all the finished clinical studies, final study reports have been submitted for assessment; for the ongoing studies, study protocols, interim reports, and/or other data available at the point of granting the Conditional Marketing Authorisation have been provided. As further data becomes available, the applicant is committing to submit those without unnecessary delay to complete the Marketing Authorisation. Similarly, all currently available quality data have been provided for assessment. Any quality data not yet available at the point of granting the Conditional Marketing Authorisation will be provided in accordance with the post-authorisation measures and the list of recommendations and specific obligations. Furthermore, safety of the product will be closely monitored, and updated data delivered. The applicant does not anticipate any reason for being unable

to fulfil the agreed post-authorisation measures but commits to notify any delay in its ability to meet the agreed deadlines.

- Unmet medical needs will be addressed.

Based on the serious impact of COVID-19 disease on public health, caused by the spread of SARS-CoV-2 world-wide, prevention of the disease is being sought through the development and use of effective vaccines. Currently, the following vaccines are authorised in the EU: Comirnaty, Spikevax, COVID-19 Vaccine Janssen and Vaxzevria. The currently authorised vaccine products have all been authorised following demonstration of a positive benefit-risk balance; however, there remains an urgent need to deliver further vaccine supplies to meet demand in both the European Union and globally. Therefore, there remains an urgent need to supply vaccines for the prevention of COVID-19 disease in the EU/EEA population, as well as to meet global demand for vaccine supplies and obligations for vaccine distribution. This includes the supply of vaccines through equal access schemes, such as the COVAX programme, co-led by the Coalition for Epidemic Preparedness Innovations (CEPI), the Global Alliance for Vaccines and Immunizations (GAVI), and WHO, which aims to provide global equitable access to COVID-19 vaccines across the globe. The increased vaccine supplies and consequent increased vaccination in EU/EEA, as well as outside of this region will help to decrease the emergence of new variants and/or its spread across the world, including the EU/EEA geographical area. The applicant therefore believes that there remains an unmet medical need for Nuvaxovid.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

Clinical evidence to date indicates that Nuvaxovid is effective in preventing COVID-19 disease. Data from various countries with high vaccination rate are showing that vaccination is not only preventing the disease of COVID-19, but also limiting the spread of the virus. The applicant considers that decreasing the number of patients suffering from COVID-19, as well as the spread of the virus, will save thousands of lives as well as have a positive impact on health care systems, both financially and by increasing capacity and focus on standard care for other diseases. It will have also positive impact on long term mental health, which deteriorated globally during the COVID-19 pandemic period. In addition, pandemic measures, depending on their severity, have significant economic impact in EU/EEA and the rest of the world. According to the WHO´s COVID-19 Strategic Preparedness and Response Plan for 2021, vaccine availability, accessibility, and deployment are the highest health, social, economic, and political priorities for virtually every country, agency, business and community around the world. The applicant intends Nuvaxovid to be used in prophylactic way to prevent disease or avoid severe cases. Therefore, the benefits to public health of the immediate availability of the product outweigh the risks of further additional data requirement.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as a dispersion for injection in a multidose vial containing 5 micrograms of SARS-CoV-2 recombinant spike protein and is adjuvanted with Matrix-M. Adjuvant Matrix-M contains Fraction-A (42.5 micrograms) and Fraction-C (7.5 micrograms) of *Quillaja saponaria* Molina extract per 0.5 mL dose. The product is provided as a multidose containing 10 doses of 0.5 mL each.

Other ingredients are: 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 product is available as 5 mL of dispersion in a vial (type I glass) with a stopper (bromobutyl rubber) and an aluminium overseal with blue plastic flip-off cap.

2.4.2. Active Substance

General Information

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.

Manufacture, process controls and characterisation

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. Evidence of GMP compliance was based on the GMP certificate issued by MHRA. This has been updated in October 2021 based on an assessment of the new facilities to be used for the manufacturing of Nuvaxovid.

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 comprehensive description of the commercial scale active substance production process performed at SIIPL is provided, comprising details of process inputs and outputs for each upstream and downstream operation unit.

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 (4.0 ± 0.1), 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.

No reprocessing is allowed. Sanitisation procedures and storage conditions for chromatographic columns are described.

Each operation unit / process step is described in sufficient detail; the corresponding operating parameters together with their ranges are indicated.

Whilst overall the process is considered adequately controlled, the applicant has committed to explore possibilities to further optimise the manufacturing process with regard to removal of impurities (**Recommendation 1**).

The batch numbering systems are adequately described. At SIIPL, the intended batch size and expected yield of active substance is stated. The conditions and transport procedures from Hadapsar to Manjari sites are adequately described.

The recommended storage temperature of SARS-CoV-2 rS Protein active substance is ≤ -60ºC.

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 The method of preparation of media, buffer, and/or solvents used in the manufacturing process along with their process scale/size, method of sterilisation (0.2 µ filtration), and storage conditions is presented. Appropriate quality agreements are in place between the applicant and the supplier of the proprietary media and supplements.

The manufacturer utilises certain single use components that have product contact. The consumables are divided into the following categories – flasks, filters, bags/containers, tubing/ancillary component. The list of single use items used is provided.

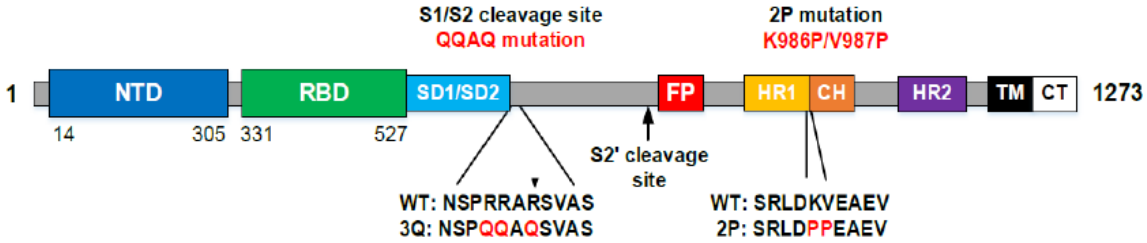
Baculovirus

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 2373)



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. The virus was harvested and filtered through 0.45 um cellulose acetate syringe filters (P0 virus stock).

The primary virus (P1) was prepared in Insect medium by infection of Sf9 cells from the WCB with virus eluted from individual plaques (P0). The P1 virus stock was selected for manufacturing of the PVS based on the rS protein expression and virus titre results. The stock vials were stored in liquid nitrogen.

The PVS (P2) was prepared in Insect medium by infection of Sf9 cells from the WCB with virus from primary virus P1. The PVS was selected for stability testing and for future GMP manufacture of the Master Virus Stock.

Data (virus titre, expression of rS protein production) show that recombinant SARS-CoV-2 rS P1 is genetically stable at least up to P6 when virus stock is produced using a specified multiplicity of infection (MOI). The applicant committed to determine the sequence for the PVS, MVS, working virus stock (WVS) and the virus in the culture harvest collected from the production bioreactor and send the report and certificates of analysis, as available (**Recommendation 4**).

The virus banking system consists of an MVS and WVS. The MVS is generated from the PVS. WVS is generated from the MVS and is the material that will be used for manufacture of the baculovirus inoculum (BVI). The MVS may also be used to make BVI. Production of a new WVS will be prepared from the current MVS Batch.

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. Future batches of WVS will be manufactured using an identical manufacturing process from the specified MVS. These future batches of WVS will be tested using release and additional characterisation tests. Analytical methods deployed for the virus stocks are sufficiently described. The testing program for the MVS and WVS includes a test for adventitious agents by Next Generation Sequencing (NGS). NGS was performed to determine if any adventitious agents are present and as a replacement for the *Ph. Eur*. *in vivo* and *in vitro* assays, animal and cell culture assays. The applicant was requested to further justify this approach taking into account the *Ph. Eur*. 2.6.16 requirements as regards the risk assessment and demonstrating/validating that the NGS method enables an unequivocal decision to be made as to whether compliance with the standards of the *Ph. Eur*. 2.6.16 monograph would be achieved if the official methods were used for the qualification/release of MVS and WVS. Further information has been provided about the (calculated) sensitivity of the NGS method using the number of genomes detected in the NGS study. According to the applicant, the level of NGS detection is between < 1 to about 450 $TCID_{50}$/mL which is said to be consistent with *in vitro* limits of detection. However, this does not seem to be consistent with published data of LOD of at least 1 $TCID_{50}$ on at least one cell line[1]. However, the NGS for testing the seed virus is considered acceptable considering that the unprocessed harvest will be tested by the *in vitro* methods. Furthermore, the applicant committed to submit the results of the ongoing characterisation of baculovirus seed virus by *in vitro*, *in vivo* and *in ovo* adventitious agents' tests January 31, 2022 (**Recommendation 2**). Also, the applicant has committed to update the risk assessment to consider all studies, justifications and technical considerations for the use of NGS testing and to ensure that it reflects the current control strategy and viral clearance study results as part of a post-authorisation commitment. This evaluation will also include comparison of the *in vitro* pharmacopeial method to the NGS test method. The risk assessment will be used to drive the analytical control strategy. The complete risk assessment is expected in Q2 2022 (**Recommendation 3**).

The release testing of the MVS and WVS has been adequately described. The applicant has committed to provide a stability testing plan for the MVS and WVS by 1 March 2022 (**Recommendation 5**).

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 in 1988 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. Beginning with a specified WCB Lot, the cells were manufactured using animal derived component free Insect medium. Prior to this lot, the WCBs were produced in Insect medium (containing cholesterol and cod liver oil).

Details are provided on the WCB preparation, including media, cell culture conditions/duration, cell passages, freezing conditions

[1] Gombold J. *et al*; Vaccine. 2014 May 19; 32(24): 2916–2926. doi:10.1016/j.vaccine.2014.02.021.

No materials of human origin were used during the pre-master cell bank or MCB manufacturing processes. Materials of biological origin include the Sf9 insect cells of the pre-MCB. In addition, the Insect cell culture medium also used other specified materials of biological origin for MCB production.

The cell bank is extensively tested for identity and absence of adventitious agents which is in accordance with *Ph. Eur*. monographs and ICH guidelines. 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. Massively parallel deep sequencing (NGS) was performed on the WCB lot in order to characterise the Sf9 cells due to reports in the literature of the presence of Rhabdovirus sequences in other Sf9 cells lines using this method. All cell banks have tested negative for viruses, with the exception of the Sf9 Rhabdovirus which is known to be present in Sf9 cells (please refer to adventitious agents section). It was sufficiently justified that additional tests for cell morphology, contaminating cells and tumorigenicity is not needed. Some further details / confirmation were requested to assure the testing of the cell bank is in compliance with the *Ph. Eur*. requirements and WHO recommendations. The viral testing strategy for the qualification of the cell banks is considered robust using cell culture techniques using appropriate detection cell lines, NGS tests and specific PCR tests for relevant viral contaminants. Overall, the testing is in line with *Ph. Eur*. testing requirement (and consistent with WHO guidelines).

A brief description of the analytical procedures deployed is provided. This is acceptable.

Data demonstrate that the MCB has remained stable for 12 years to date. Studies using end-of-production cells support the use of the Sf9 cell line for active substance production. The applicant has further clarified and justified the control of maximum passage level during routine production.

Control of critical steps and intermediates

Critical process parameters (CPPs), in-process controls (IPCs) and critical quality attributes (CQAs) are defined. An assessment of the quality attributes of SARS-CoV-2 rS protein active substance was performed after Phase 3 clinical trials, including the analytical tools available to monitor those attributes and the strategy for using the tools. Evaluation of QAs is based on risk assessment using the principles of Quality by Design (QbD) described in ICH Q8, Q9, Q10 and Q11. In general, relevant QAs are discussed and classified as CQAs.

During development of the SARS-CoV-2 rS manufacturing process, a risk assessment was performed to identify process parameters that have the potential to affect product quality or process performance when varied from their set point. Process parameters (inputs) that were identified to impact product quality (based on their potential to impact a CQA) were given a presumptive classification of "critical" and were included in the Process Characterisation plan. Parameter operating ranges were defined through process development experimentation and by leveraging platform knowledge gained through respiratory syncytial virus (RSV) fusion (RSV-F) and quadrivalent Nanoparticle Influenza Vaccine (qNIV) active substance process characterisations.

All process control and performance parameters are listed. If the results for critical process controls are outside of the acceptable ranges or limits, a deviation will be raised and an investigation of the deviation event will be performed, including an assessment of any potential impact on product quality. The disposition decision will be determined based on the outcome of the deviation investigation.

The following attributes are controlled to maintain the quality and specification of the active substance: control of starting materials viz., use of well-characterised Sf9 cell banks and recombinant baculovirus

stocks/ virus seeds, control of incoming raw materials and components/ consumables, control of design of the manufacturing process and operating process parameters and in-process controls.

For each operation unit/step, the set points, normal operating range (NOR), proven acceptable range, and parameter type/classification (non-key process parameter (NKPP), key process parameter (KPP), key process attribute (KPA)) for each process parameter (PP) is indicated together with a range justification. The NORs, PARs, and target set points are established using process characterisation studies and manufacturing process data. Justification has been provided about the classification of PPs and IPCs.

Hold times for BVI and in-process pool materials are sufficiently supported by process characterisation/validation studies. Based on the hold time study, the proposed hold times for the BVI and intermediates can be considered conservative.

Process validation and/or evaluation

A stepwise strategy for defining and validating the manufacturing process of the active substance produced at SIIPL through the process life cycle, i.e. stage 1 - process design, stage 2 - process qualification, stage 3 - continued process verification following process performance qualification (PPQ) throughout the commercial life cycle of the product).

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.

Two process validation studies were conducted at SIIPL at the commercial scale utilising cell culture medium A and cell culture medium B.

Each analytical procedure was selected based on the knowledge acquired through the combination of characterisation, manufacturing history, clinical experience and safety and quality requirements. Validation of analytical procedures was performed in accordance with the principles outlined in ICHQ2(R1).

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. The presented HCP clearance studies showed significant HCP reduction by the active substance purification process. However, the reported HCP values did not represent the absolute HCP values as the applied assay has previously shown non-specific reactivity and as such was not reliable for absolute quantitation. The assay for HCP is under development. When the suitable assay is qualified, it will be used to demonstrate in-process HCP clearance (**Recommendation 17**). HCP levels were investigated at the active substance level by peptide mapping/mass spectrometry (MS) and SDS-PAGE (please refer to discussion on comparability and characterisation). It is noted that the studies in support of impurity removal capability for other process-related impurities were performed at another specified site which is not part of the MAA. It has been demonstrated that the conclusions reached from these small scale studies confirming satisfactory process removal capacity for process-related impurities are also applicable to the commercial SIIPL process. The applicant has committed to submit the pending spiroplasma test results for the Bioreactor

Crude Harvest post-authorisation (**Recommendation 6**). In addition, the applicant has committed to provide the PPQ HCP-data when available (**Recommendation 7**) and to submit a protocol describing the resin lifetime verification at full scale (**Recommendation 8**).

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. Each process performance qualification study met the pre-defined acceptance criteria in the respective study protocol with the results demonstrating a controlled process that is deemed validated. 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 (**Recommendation 1**). Demonstration of the process remaining in a state of control will be conducted through continued process verification.

Manufacturing process development

Extensive information is provided about the manufacturing process development. The active substance processing steps were developed based on the platform technology that Novavax has used for other vaccine candidates including RSV-F and qNIV.

The active substance manufacturing process development is complex and comprises batches produced for clinical studies and qualification of the commercial process. These batches have been produced at multiple sites using different versions of the active substance manufacturing process.

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.

Non-Clinical Batches Produced at Novavax

The information provided on the non-clinical batches is limited to lot name, date of manufacture, amount produced and estimated purity (SDS-PAGE). However, the active substance process applied for these non-clinical batches was based on the process developed for the RSV vaccine with slight adaptations which are unlikely to impact on the quality profile when compared to the material used for the first clinical studies. With the vast experience gained from the phase 1, 2, and 3 human clinical studies, there seems little merit in requesting further quality related information for the non-clinical batches.

Manufacturing Process Changes for Batches Produced at Emergent (EBSI)

Changes implemented between batches within the active substance manufacturing campaign for clinical trial supply were assessed to have a low risk of impacting product safety and quality. The changes introduced during the EBSI campaign concerned harvest start criteria, harvest method, increase in cell density target for dilution, changes to the cell lysis step, and a change in virus stock used to infect the production culture from MVS to BVI.

Manufacturing Process Changes for Batches Produced at *Fujifilm Diosynth* (*FDBU)*

The identified changes for the transfer of the manufacturing process from EBSI to FDBU commercial scale were deemed to be low or no risk requiring no mitigation strategy to demonstrate no product quality impact. Changes were introduced at the stage of Sf9 cell culture (upscaling), BVI preparation, harvesting method, low pH treatment of cell lysate, changes in clarification process, several changes in chromatographic and filtration steps and increase in active substance target concentration. Most

changes were aimed to increase production capacity and increase of product purity. Changes were also introduced into the control strategy to further assure process robustness.

Manufacturing Process Changes for Batches Produced at Serum Institute of India (SIIPL)

The process was transferred to SIIPL. For commercial purposes, SIIPL has scaled-up the active substance process. Additional changes were made to the baculovirus production (scale-up) and infection step (reduced MOI), cell culture media, harvest and clarification procedures and a change to the supplier of an excipient.

Demonstration of comparability

In order to demonstrate comparability of the active substance from different manufacturing sites, the applicant established the following approach. Each lot was assessed against the current version of the appropriate lot release protocol for the active substance. All lots had to fall within the lot release acceptance criteria for the site. In addition, characterisation data were compared to characterisation data from at least three active substance PPQ lots. Results from characterisation assays were expected to fall within the specified acceptance criteria to be considered comparable.

A direct comparison between EBSI (clinical batches used in clinical studies 2019nCoV-101 (Phase 2 AU/US) and 2019nCoV-302 (Phase 3 UK)) and SIIPL process/product is not available. The applicant's strategy was to demonstrate comparability between EBSI and FDBU (pre-PPQ clinical material used in 2019nCoV-101 (Phase 2 AU/US) and 2019nCoV-301 (Phase 3 US/MX)), between FDBU pre-PPQ and PPQ and between FDBU PPQ and SIIPL. Indirectly, the comparability between EBSI and SIIPL would then be substantiated. The rationale for this staged approach is that clinical trials in US and Europe were similarly staged i.e. initiated using EBSI material and then using FDBU material in the US/Mexico Phase 3 trial. Comparability was therefore initially assessed between EBSI clinical material and FDBU clinical material.

Active substance comparability studies included both active substance batch release tests and additional characterisation tests.

A comprehensive set of physico-chemical and biological analytical methods have been applied which cover quality attributes relevant for the demonstration of comparability.

Comparability between EBSI and FDBU

Multiple changes were introduced during active substance process development, the overall process remains the same across sites. For each change the rationale and risk assessment is provided which are overall considered acceptable.

Several changes have been introduced at the upstream and downstream stages which increased product purity.

Extensive comparability testing results are provided and discussed in more detail. The number of batches are generally considered sufficient to reach a conclusion on comparability between the materials.

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).

Purity (expressed as %rS and %gp64) is tested by peptide mapping/mass spectrometry (MS) and is considered indicative of an overall higher gp64 content in the FDBU lots when compared to EBSI lots.

According to the applicant, the HCP identification (MS) showed that the predominant impurity for the FDBU lots is gp64 whereas the predominant impurity for the EBSI lots is an Sf9 protein which is also present in FDBU lots at lower levels. However, multiple other baculovirus related and other HCPs were detected. As such, the purity cannot be determined only by the percentage of gp64 present. It is noted that both EBSI and FDBU materials were used in the Phase 2 and 3 clinical trials and as such the purity profiles of both EBSI and FDBU materials are supported by the safety data obtained and considered to be clinically validated.

There are differences in average particle size, size distribution and higher order oligomer content between the EBSI and FDBU materials. According to the applicant, particle size and morphology of the active substance have a moderate impact on efficacy. Active substance particle formation is reversible and dependent on formulation conditions, temperature, and time. The risk of impact on clinical performance is considered to be low as Phase 3 clinical experience is available covering a wide range of particle size and morphology.

There is a higher potency trend seen in FDBU lots which could be related to the potency assay (ELISA) applied. While there is a higher relative range for the FDBU lots as compared to the EBSI lots using the original binding ELISA, all FDBU lots used in the clinical trial were within the original limits of the ACE2 receptor binding ELISA assay.

Comparability between FDBU pre-PPQ and PPQ

Multiple Phase 3 clinical studies were conducted using pre-PPQ active substance material produced at FDBU. The changes introduced between pre-PPQ and PPQ are limited and mainly in the upstream processes. The totality of the data for all of these analyses demonstrates overall comparability of the materials manufactured at FDBU prior to PPQ and the materials produced for PPQ.

Comparability between FDBU and SIIPL

Data from the active substance PPQ lots produced at SIIPL were compared against those generated for the FDBU PPQ lots, thereby creating a link back to the clinical trial material.

The most notable difference in the results for various lots is the higher potency (as tested by hACE2 receptor binding ELISA) and faster binding kinetics association rates for the SIIPL lots compared to the FDBU lots. According to the applicant, the slight increase in active substance potency is not likely to affect the efficacy of the vaccine and needs to be considered in the context of acceptable finished product potency justified by clinical studies and process performance capabilities. The applicant considers that minor differences observed in the k_a (association/binding) rate for different active substance lots produced at different sites are most likely due to the assay variability and not due to differences in the quality of the active substance.

As regards to active substance purity (as measured by peptide mapping/MS taking only protein impurity gp64 into account), the applicant considers that the SIIPL PPQ lots fell well within the range of rS content tested in the clinical studies and that, while lot to lot differences can be seen, on average, the PPQ lots from both FDBU and SIIPL manufacturing sites are considered comparable. When considering all protein impurities, and not only gp64, SIIPL batches do seem more pure than FDBU (and EBSI), both by peptide mapping/MS and SDS-PAGE. The purity data for EBSI batches are not directly comparable with FDBU and SIIPL batches as different methods have been used. EBSI batches are not available anymore for retesting. The FDBU and SIIPL batches have been tested with the SDS-PAGE method that is used for release. The FDBU batches represent a worst-case situation with purity for specified lots.

It is concluded that the SIIPL 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.

Similarly, it is concluded that the 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. According to ICH Q5E, in these circumstances, pre- and post-change product can be considered comparable. 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. In this respect, it should be noted that 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, but comparability regarding average particle size is uncertain. This is however not expected to have an impact on safety or efficacy.

The applicant has further justified why the trimeric nature of the protein has not been addressed for comparability. The Gen1v2 potency assay specifically measures binding of hACE2 receptor dimers to protomers within the rS trimers and is considered the key functional assay to ensure proper folding of rS and integrity of the receptor binding domain. Potency testing is included in all analytical comparability studies.

Characterisation

Structural characteristics of the rS protein have been investigated using different orthogonal methods. Characterisation studies were performed with EBSI and FDBU active substance. An overview of the batches included in the different characterisation studies has been provided. No SIIPL batches were included in the analysis. However, most of the methods that were used for characterisation were also used for the comparability assessment between FDBU and SIIPL batches.

Primary structure: SDS-PAGE showed a main band between 98 and 198 kDa, which was detected by the antibody on Western blot and thus confirmed the identity of the rS protein. Peptide mapping with MS revealed the correct primary structure. A longer hydrophobic domain near the C- terminus amino acid 1192 – 1245) was not confirmed by peptide mapping MS, the applicant has committed to develop an improved method and provide further data on the C-terminus peptide (**Recommendation 11**). Furthermore, it was shown that 18 out of 22 glycoform attachment sites were glycosylated with high mannose or pauci-mannose structures. Deamidation and succinylation was detected at Asn501 and methionine oxidation was not detected. Oligosaccharide profiling by HPLC-FLD confirmed that the glycoforms were mainly high mannose (Man3F) and pauci-mannose forms. The data presented from three EBSI and three FDBU batches indicates that the EBSI and FDBU batches have slightly different oligosaccharide abundance; the FDBU batches contain more Man3F and Man3 and less Man8 and Man9 than the EBSI batches. The applicant has committed to characterise the glycosylation profile for the next 10 batches manufactured at SIIPL and based on the data obtained to present an evaluation on the need for any further monitoring or control of the glycosylation profile (**Recommendation 12**).

The secondary structure was revealed with Far-UV circular dichroism (CD) and differential scanning calorimetry (DSC). The DSC revealed improved thermal stability over the native S-protein. Secondary structure as revealed by Far-UV CD and DSC was comparable between EBSI and FDBU batches. No verification of the secondary structure by confirmation of the expected disulphide bond configuration has been provided. The applicant has committed to develop a method to confirm the expected disulfide bonds (**Recommendation 13**).

Higher order structure was investigated by Size Exclusion Chromatography coupled with in-line UV and Multi-Angle Light Scattering detection (HPSEC-MALS) and Asymmetrical-Flow Field-Flow Fractionation with MALS detection (AF4-MALS). The active substance is expected to be comprised of rS trimers, dimers of trimers, and other oligomeric forms. This was confirmed by the HPSEC-MALS chromatograms, in which a continuum of oligomeric rS forms was seen and by the AF4-MALS chromatograms, in which a broad population of large particles was observed. Differences in the HPSEC-MALS chromatograms were observed between EBSI and FDBU batches. In addition, capillary electrophoresis - sodium dodecyl sulfate (CE-SDS) data and SDS-PAGE data provide information on size heterogeneity of the rS active substance. Non-reduced CE-SDS shows, according to the applicant, three major peaks that correspond to molecular weights expected for monomer, dimer, and trimer forms of rS in the vaccine. However, the MW information for CE-SDS has not been verified by the use of protein standards. Based on this an improved CE-SDS method is under development, which is different than the CE-SDS method used during the early stage of development. The applicant has committed to develop this CE-SDS method and provide identification of the peaks in the final electropherogram and to include a discussion of the data and final confirmation of the molecular weights (**Recommendation 14**). Similarly, the HPSEC-MALS method under development is intended to provide a qualitative assessment of the various structures present in the active substance and not to address the distribution of monomeric, dimeric, and trimeric forms of rS. The applicant has committed to develop the HPSEC method further to normalise protein concentrations prior to sample injection and to include the use of appropriate molecular weight standards (**Recommendation 15**).

Particle characteristics were investigated by Dynamic light scattering (DLS), Nanoparticle tracking analysis (NTA), Negative-stain transmission electron microscopy (TEM) and Single-particle cryo-EM. The DLS analysis showed that hydrodynamic diameter of rS particles from EBSI batches was smaller than from FDBU batches. EBSI batches were more homogenous, and FDBU batches showed more polydispersity. The TEM analysis demonstrated that 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. With Cryo-EM, intertrimer interactions between rS proteins were observed resulting in higher order spike multimers.

A summary of the current knowledge on particle morphology has been provided and the main conclusions made are: 1) The key immunologic component of the active substance is the rS trimer, 2) The particles are dynamic and help to preserve rS in a soluble state in the active substance, 3) Particle morphology for the active substance, within the manufacturing process variability, is not linked to finished product immunogenicity and therefore not considered to be a CQA.

Physico-chemical properties: The development of an MS method for confirmation of MW is ongoing (**Recommendation 16**). Existing data confirming the theoretical extinction coefficient as well as information on protein content was provided.

The biological functionality of the rS protein was confirmed by measuring the rS binding to hACE2 receptor by biolayer interferometry (BLI) and by ELISA, and by a mouse model of immunogenicity to demonstrate the ability of rS to elicit functional and neutralising antibodies. BLI revealed a very tight binding between the rS protein and the ACE2 receptor. The mouse model of immunogenicity showed that rS protein in EBSI lot DS2 was immunogenic and elicited functional antibodies in mice (anti-S IgG, hACE2-receptor binding inhibiting antibodies, and neutralising antibodies). The mouse immunogenicity method has been revised and several studies using force-degraded rS to evaluate whether this assay is capable of distinguishing sub-potent batches has been conducted. In studies, this mouse immunogenicity model distinguished between intact and degraded samples in mice immunised with a low dose of rS with Matrix-M adjuvant in a manner that generally corresponded with the *in vitro*

potency measures. The mouse immunogenicity test is not intended for use in product release, comparability evaluation, or stability testing and will be used as a research investigational tool.

Product-related impurities

In forced degradation studies, a decrease in the binding assays (ELISA, BLI and protein ELISA) without an effect on particle size (by DLS and HP-SEC) and fragmentation (SDS-PAGE and Western Blot) is observed after exposure to high pH (8.5), whereas after exposure to low pH an effect on the binding assays, and increase in particle size and degradation on SDS-PAGE and Western Blot is observed. Thermal stress also had a significant effect on binding assays, and resulted in an increase in particle size, but without an effect on degradation. Proteolysis had an effect on all assays but less on the protein ELISA, which is a monomer-specific ELISA, showing that the binding of the monomer was less affected. Oxidation, freeze-thaw and agitation did not affect any of the assays. There is no strong correlation between deamidation or succinimide post-translational modifications and biological activity, and a more general disruption of epitopes in rS protein during thermal stress is likely the cause of decrease in biological activity. The oxidation, deamidation and succinimide variants are considered product-related substances. In summary it can be concluded from the forced degradation studies that the binding assays and DLS are stability-indicating assays.

Stressed samples were selected for *in vivo* evaluation to determine the correlation between *in vitro* and *in vivo* potency. A good correlation exists between *in vivo* and *in vitro* potency, except for the sample that was degraded by proteolysis. Although *in vitro* potency was decreased, the fragments were still immunogenic.

Regarding fragments, the applicant clarified that low molecular weight species (~140 kDa) observed correspond to the theoretical molecular weight of the unglycosylated spike protein and are not considered a fragment. Other low molecular weight species are present in low amounts and therefore not of concern. The low abundance of monomeric form of rS has been verified by a monomer-specific ELISA quantitation assay.

Process-related impurities

On SDS-PAGE the most abundant protein in active substance batches besides the rS protein is the baculovirus (BV) gp64 protein. In addition, other LMW bands are visible on high load SDS-PAGE gels. The SDS-PAGE shows that more gp64 is present in FDBU batches than in EBSI batches and in EBSI batches greater quantities of other HCPs and other BV proteins are present than in FDBU batches. For gp64 this was confirmed by (semi-quantitative) Mass Spectrometry.

Other residual host cell (Sf9) proteins and baculoviral proteins were evaluated using a proteomics-based HCP-MS method. Relevant HCPs and the abundance in the pre-PPQ and PPQ FDBU batches have been identified. Gp64 is the most abundant HCP from BV, and the only other BV protein seen among the top 15 most abundant proteins. There are 5 host cell proteins (Sf9 and BV combined) above a 1% relative signal intensity in all batches investigated. From the data presented, it is clear that the gp64 is the most abundant HCP for most batches. However, there are differences from batch to batch in which HCPs are most prevalent when considered relative to the total Sf9 and BV proteins identified.

For release, purity is assessed by SDS-PAGE combined with densitometric scanning. No other methods for the estimation of purity and impurities are in place. During the procedure a major objection was raised in relation to limitations of the proposed control of purity and the applicant was asked to provide further evidence that SDS-PAGE with densitometric scanning is a sufficiently quantitative and accurate method to control purity. In addition, the applicant was asked to further justify the proposed specification limit and to develop additional methods for control of purity. In response, the applicant provided additional data and justifications to support the SDS-PAGE method suitability and proposed acceptance limit.

The release test for purity is an important test to control on the one hand the amount of rS protein that will be present in the finished product (in combination with total protein), and on the other hand the level of impurities, like HCPs. Only impurities above the limit of quantitation will be included in the overall purity calculations by SDS-PAGE. Initially there was a concern that several different impurities are present at or below the limit of quantitation, which altogether contribute substantially to the level of impurities, but remain undetected. However, the proposed control of purity using the SDS-PAGE method is considered acceptable, based on the considerations below:

An acceptable safety profile has been shown for the FDBU batches tested in clinical studies. These batches are considered worst-case with respect to impurity levels, compared to commercial batches. In addition, five-time higher doses of 25µg also showed an acceptable safety profile (see manufacturing process development section for further details). The FDBU and SIIPL batches have been tested for purity with the SDS-PAGE method that is used for release. The FDBU batches represent the worst-case situation. Considering the purity levels of the batches used in clinical studies, and the purity levels of SIIPL batches, the specification for purity of rS content is acceptable.

HCP assessment via MS is currently being evaluated to characterise the 7 most abundant HCPs (including gp64) observed in the active substance. The applicant committed to implement the method and set preliminary specification limits already after testing 10 active substance lots (**Recommendation 18**). This test will provide additional control on impurities. A comparison between MS and SDS-PAGE data for both FDBU and SIIPL active substance lots will be provided (**Recommendation 22**). Until the MS method can be implemented, gp64 is controlled through the SDS-PAGE method currently used for active substance release. Justified acceptance criteria are proposed based on the data available. Furthermore, a CE-SDS based purity method and HCP ELISA will be developed (**Recommendations 14 and 17**). Additionally, rS integrity is controlled also by the potency testing. In the presence of the strong adjuvant there is a theoretical concern of immunological molecular mimicry, potential induction of an immune response against the epitopes on these proteins. To address this theoretical concern, the most abundant HCP / HVP will be screened for an overlap in epitopes with human proteins (**Recommendation 10**).

Considering the additional data and justifications provided and noting the commitments of the applicant to further improve the control of purity and impurities, the major objection raised was considered resolved.

Levels of DNA in the active substance batches are low and therefore considered to be acceptable, both for total DNA and for BV DNA and sf9 DNA. It is acceptable that DNA levels at release are controlled by Total DNA using picogreen detection.

Infectious baculovirus is controlled at release. The detection limit of the plaque method is acceptable.

The active substance contains polysorbate 80 and phosphate buffer and an investigation regarding low endotoxin recovery (LER), including spike-recovery studies will be performed to further confirm absence of endotoxin. (**Recommendation 21**).

Conclusion

Overall, sufficient information on the characterisation of the molecule has been provided to support the conditional marketing authorisation. A number of post-authorisation commitments have been agreed with the applicant (recommendations) to provide data to further substantiate this conclusion.

Specification

The active substance specifications include general tests (appearance, pH, PS-80), protein concentration, identity (by western blot), purity (SDS-PAGE), potency (ELISA), residual DNA and safety tests (endotoxin, bioburden, mycoplasma/spiroplasma, harvest contamination).

For release, purity is assessed by SDS-PAGE combined with densitometric scanning. Please refer to the characterisation section for a discussion on the control of purity. The applicant is also recommended to implement a shelf-life specification for purity by SDS-PAGE (**Recommendation 24**). Upon introduction of the CE-SDS method for purity testing the applicant should also implement justified acceptance criteria for active substance and finished product release and stability testing (**Recommendation 14)**.

Identity is controlled by Western Blot, which is considered acceptable.

The applicant is recommended to re-evaluate the total protein specification limits when 30 commercial scale lots have been manufactured **(Recommendation 23).**

Potency testing is performed with an ELISA in which the amount of rS protein that binds to the hACE2 receptor, which is coated on the plate, is measured. Potency is established relative to a reference standard. Throughout development, the ELISA assay was improved. Notably, Zwittergent was added to diminish interactions between the trimeric proteins and PS-80 that could influence the potency estimation for active substance batches. Active substance batches manufactured at FDBU and at SIIPL have been retested with the improved assay, using the same reference standard and thereby allowing a comparison between the potency results of FDBU and SIIPL batches. The potency of SIIPL batches were higher than the potency of FDBU batches, possibly caused by the higher purity of SIIPL batches. Potency results of batches of both manufacturers have been used to establish the acceptance criteria which is considered acceptable.

Contaminant testing is performed at the harvest level by bioburden testing. Adventitious agents testing is performed by cell culture method on 4 cell lines.

Analytical methods

For compendial methods, the type of procedure is mentioned and reference is made to the *Ph. Eur*. Non-compendial methods are described in sufficient detail. For all methods acceptable system suitability criteria are provided and the preparation of standards and samples is described. Methods are validated in line with ICH Q2 (R1). For some methods additional validation data remain to be submitted (**Recommendations 19 and 20**).

Batch analysis

Batch analysis data of active substance batches manufactured as SIIPL (n=6) has been provided. The results are within specifications and confirm consistency of the manufacturing process.

Reference materials

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. Please refer to the finished product section for further discussion on this point.

Container closure system

Adequate information is provided on the container closure system. The dossier includes references to relevant *Ph. Eur.* monographs for the primary packaging materials. The active substance is stored in sterile, single-use Flexible Freeze Thaw Bags at ≤ -60 ºC. The FFT bag is chosen based on the established historical extractable and leachable data provided by the supplier and additional Novavax studies performed in the context of a previous product development. Extractables and leachables studies have been performed under worst-case conditions, the results being acceptable from a toxicological point of view. The choice of the container/closure is justified, also based on the results of active substance stability studies. It has been sufficiently demonstrated that the container closure system provides adequate protection from microbial contamination.

Stability

The proposed shelf life for the active substance is 9 months stored at <-60 ºC.

Stability studies on an adequate number of active substance batches produced according to the commercial process are on-going and available results were provided. Studies have been performed in accordance with relevant ICH stability guidelines.

Two batches of SARS-CoV-2-rS active substance manufactured at FDBU together with 6 batches manufactured by SIIPL were placed on stability. The batches were manufactured according to the proposed commercial process and filled in the proposed commercial container closure system.

A description of the stability batches is provided. The primary stability batches are under evaluation at real time (Long term) storage conditions of ≤ -60 ºC and accelerated conditions (5 ºC ± 3 ºC). Relevant quality attributes are part of the active substance stability testing protocol, including tests for appearance (colour, clarity, particulates), pH, protein concentration, purity (SDS-PAGE), potency (ELISA) and identity (Western Blot). It is noted that the SIIPL batches placed on stability are additionally tested for PS80 content, total DNA and residual infectious baculovirus. It is questionable whether the latter two can be considered stability indicating. The applicant has been requested to introduce a stability test for control of particle size, such as DLS. As the DLS method is currently not validated, the applicant has committed to initiate the method development and validation work with a target completion date of Q3 2022. In the meantime, particle size for SIIPL will be monitored in order to establish an appropriate release and shelf-life specification for the z-average particle size (**Recommendation 38**).

FDBU active substance lots remain within specification after 9 months when stored at long-term conditions (-70ºC ± 10ºC). No significant changes in purity (SDS-PAGE) are discernible under these conditions.

Limited stability data is available for the PPQ lots produced at the commercial site, SIIPL.

Stability testing results are available for FDBU samples stored under accelerated conditions (5°C ± 3°C) conditions and stress conditions (25% ± 2/60% ± 5% RH for 1 month and at 40° ± 2°C/75% ± 5%RH for 1 week). For SIIPL lots limited data is available for samples stored at 5°C ± 3°C.

As concluded in the manufacturing development section, FDBU and SIIPL lots cannot be considered fully comparable as regards to purity and potency. Hence, the FDBU stability data cannot be considered fully supportive until further data is provided. In this respect, it is noted that thermal stress studies are underway and will be used to confirm that the degradation products and rates are comparable between active substance produced at FDBU and SIIPL. Assays included appearance, pH, SDS-PAGE (purity), Protein Concentration (SoloVPE), potency ELISA and DLS (**Recommendation 9**).

In addition, one batch of SARS-CoV-2 rS active substance will be placed on stability each year.

Stability studies will be conducted at ≤-60 ºC (long term conditions) for annual testing and under accelerated conditions at 2-8 ºC, if a significant process change is made.

The applicant has committed to report any unexpected trends or out of specification results for the on-going stability studies for FDBU and SIIPL lots. Updated stability data for active substance samples stored under long-term and accelerated conditions are awaited in January 2022 (**Recommendation 25**).

Overall, limited data have to date been provided in support of the proposed 9 months shelf life for active substance when stored at <-60 ºC. However, considering the initial data provided and the low temperature proposed for long-term storage it is not expected that the quality of the vaccine will be significantly impacted during storage under these conditions. Therefore, in conclusion, the 9 months shelf life for active substance when stored at <-60 ºC is considered to be acceptable.

2.4.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Description of the product

The finished product is a sterile, preservative-free, aqueous buffered dispersion for injection containing the SARS-CoV-2 rS protein as active substance. The active substance is co-formulated with Matrix-M1 adjuvant and presented in a multi-dose vial (minimum 6.1 ± 0.1 mL fill) containing ten doses of 0.5 mL. The formulation buffer contains sodium phosphate heptahydrate and monohydrate, sodium chloride and polysorbate 80 and additional excipients for the adjuvant are cholesterol, phosphatidylcholine, potassium dihydrogen phosphate and potassium chloride. The excipients comply with appropriate compendial standards, except for a few components which are controlled by in-house specifications. 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.

[2] Matrix-M consists of Fraction-A (42.5 micrograms) and Fraction-C (7.5 micrograms) components and the excipients of cholesterol, phosphatidylcholine, potassium dihydrogen phosphate, potassium chloride, disodium hydrogen phosphate dihydrate, sodium chloride, and water for injections.
[3] Phosphatidylcholine contains 0.1 – 0.2% α-Tocopherol (all-rac-α-Tocopherol) (according to the specification).
[4] There are no Ph. Eur. and BP monographs for Disodium Hydrogen Phosphate Heptahydrate. Disodium hydrogen phosphate heptahydrate referred to as Sodium phosphate dibasic heptahydrate on supplier CoA. Sodium dihydrogen phosphate monohydrate referred to as Sodium phosphate monohydrate monobasic on supplier CoA.

The recommended storage conditions of finished product is 2°C to 8°C and the intended route of administration is intramuscular injection.

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
Matrix-A and Matrix-C contain purified, chromatographic fractions (A and C) of enriched purified bark extract from the tree *Quillaja saponaria* Molina, as well as cholesterol, from botanical origin, and phosphatidylcholine, from hen's egg yolk. The Matrix-A and Matrix-C adjuvant components, assembled from a specified and controlled batch formula of saponin, cholesterol and phosphatidylcholine, are regularly shaped, uniform and stable complexes (nanoparticles). Matrix-A and Matrix-C are nanoparticles suspended in phosphate buffered saline (PBS). Cholesterol and Phosphatidylcholine are present as excipients in the Matrix solutions.

The processes of Fraction isolation and Matrix formulation have been described in sufficient detail. The controls of the materials used for the manufacture of both Matrices are acceptable. The process control strategy is based on a failure mode and effects analysis (FMEA) risk assessment and is appropriate.

The impact of technical transfer and scale-up of Matrix-A and Matrix-C product has been adequately evaluated by comparing analytical data of the matrices produced by processes performed at AGC-Copenhagen, AGC-Seattle and Novavax, Uppsala to analytical data obtained from analysis of Matrix-A and -C produced at a validated smaller scale process at Novavax, Uppsala (used for clinical study material).

Characterisation has been conducted with several orthogonal methods for chromatographic profile (RP-HPLC-UV), identity (HPLC-MS, 1H-NMR, 2D NMR), monosaccharide analysis , haemolytic activity, particle size (DLS, Multi-angle DLS), and structure (TEM).

The impurities related to the manufacture of Matrix A and C have been adequately discussed. Forced degradation studies show that Matrix-A and Matrix-C are robust formulations.

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 SA/PC, bioburden and endotoxins. A suitable justification has been provided for replacing a haemolytic activity test with the test for cholesterol/saponin ratio. The proposed tests are acceptable. The applicant has committed to revise the specifications when more batch data are available and to merge the currently separate release and shelf-life specifications into one single specification **(Recommendation 45)**. The shelf-life will also be reviewed based on the updated specification and stability data **(Recommendation 46)**.

Adequate information has been provided for the reference standards used in the analysis of Matrix-A and Matrix-C.

Adequate information on the composition, quality references and control of the two container closure systems for the matrices has been provided. The applicant is however recommended to update the

control specifications to further align with the Guideline on plastic immediate packaging materials **(Recommendation 44)**. In view of the conducted initial risk analysis, the gap analysis for the polyethylene terephthalate glycol (PETG) bottle packaging components and the toxicological evaluation of extractables, the risk of critical presence of leachables in the matrices is considered low. The initiated leachables study is appropriate. The post-authorisation commitment to submit the report of the 2-year leachables study for the PETG bottle is acceptable **(Recommendation 42)**. In view of the conducted risk assessment and compliance of the contact layer ultra-low density polyethylene (ULDPE) with *Ph. Eur*. 3.1.5, the risk of presence of critical leachables in the matrices is also considered low for the ULDPE biocontainer bags. The protocol of the verifying study is acceptable **(Recommendation 43)**. The post-authorisation commitment to submit the results of the study is acceptable.

The proposed shelf life for Matrix-A and Matrix-C is acceptable based on real time (5±3°C) stability data from six batches of Matrix-A and three batches of Matrix-C manufactured at Novavax. For the commercial scale batches, 6 months results are available (5±3°C and 25 °C/60% RH).

Pharmaceutical development

The finished product presentation has evolved during clinical development. For the Phase 1/2, Part 1 study, SARS-CoV-2 rS antigen was filled separately and used for bedside mixing with Matrix-M1 adjuvant prior to administration. All follow up clinical studies were performed using SARS-CoV-2 rS pre-mixed with Matrix-M1 adjuvant. The overall composition of the formulation buffer remained the same throughout the development to the commercial stage, with only differences in the ratio of monobasic to dibasic sodium-phosphate salts and differences in PS80 grade used.

Formulation development started with exploring three different formulations based on other recombinant vaccines and the most optimal one was selected for further development. Subsequently, variations in the formulation composition were studied with the objective of optimising the selected formulation. Results of these formulation studies indicate that the initial formulation was the optimal formulation for minimising loss in potency and aggregation of the SARS-COV-2 rS antigen. No additional work was done to develop a formulation containing a preservative. This is understandable and acceptable in view of the urgent need for Covid-19 vaccines. Exploratory stability studies were subsequently performed to select suitable glass vials of different suppliers.

The presented in-use stability studies indicate adequate physico-chemical stability of left-over finished product (after removal of 9 doses) in Type I glass vials during the proposed 6-hour in-use shelf-life at 2-25 °C. One of the specified vial types will be used for commercial production at SIIPL. The applicant is recommended to conduct further evaluation to confirm whether or not the upper limit of the finished product pH range is relevant for compatibility. (**Recommendation 36)**.

The applicant provided a study demonstrating that long lasting agitation results in an increase in particle size and particle size distribution and causes some damage to the trimer spike proteins. The applicant is recommended to perform a shipping qualification study in order to evaluate the real-world impact of movement/ vibration/ agitation on the quality of the vaccine **(Recommendation 26).**

It is noted from the Applicant's information that Matrix-M1 adjuvant is prone to stability issues (aggregation) in some glass vials due to leaching of silicon and boron. Therefore the applicant has provided data to demonstrate that the selected vials are compatible with Matrix-M. Differences in glass quality between compatible and incompatible glass vials can be identified by the expansion coefficient of the glass.

Manufacturing Process Development Overview

Formulated finished product for use in early phase clinical studies was manufactured at EBSI at a suitably defined batch size.

The finished product batches used in the two pivotal 2019nCoV-301 and 2019nCoV-302 are provided. Two finished product lots manufactured at EBSI were used in the Phase 3 clinical study in the UK. The active substance used for EBSI finished product lots was manufactured by EBSI.

Two finished product lots that were used in the clinical Phase 3 studies in US/Mexico have been manufactured at Par Sterile Products (PAR). The manufacturer of active substance for PAR lots was FDBU.

The finished product manufacturing process employed at SIIPL was developed based on prior product knowledge and manufacturing technology received from Novavax. The process is conducted in a fill-finish plant, which routinely fills other vaccines (primarily COVID-19 vaccines) into a similar container closure configuration and has also a historical record of aseptic process and practices. The process knowledge and practices are followed at the Manjari site for commercial scale manufacture. In order to complete the comparability exercise, an analytical comparability study was completed for the batches manufactured at EBSI and PAR used in the clinical studies. The strategy to demonstrate comparability of finished product manufactured at SIIPL to finished product lots used in the clinical studies is shown in Figure 2.

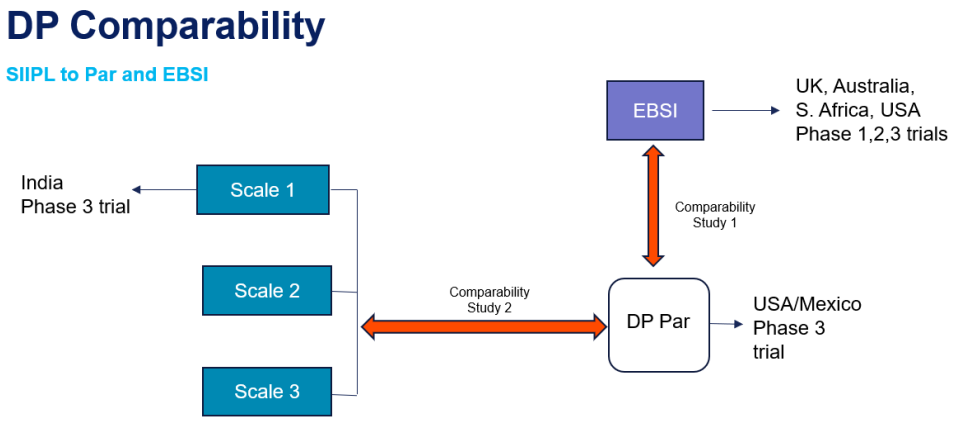


Figure 2: Comparability between finished product Manufactured at EBSI and PAR

Two lots manufactured at EBSI (material used in the phase 3 UK study) and two lots manufactured at PAR (material used in the phase 3 US/Mexico study) were included in the first comparability study.

Besides the origin of the active substance, the major changes in the finished product process between EBSI and PAR include the antigen formulation target concentration, the manufacturing scale, and the vial (single dose versus multidose vials).

Analytical methods used for comparability are finished product release tests (appearance, pH, osmolality, total protein, potency by SARS-COV2-rS binding ELISA Gen1v1, identity by western blot, Matrix-A content, Matrix C content, sterility, endotoxin) and additional characterisation tests. i.e, cholesterol concentration, phosphatidylcholine concentration, saponin integrity, particle size by dynamic light scattering, negative stain TEM and 2D class averaging, microflow imaging and nanoparticle tracking analysis. In addition, degradation of finished product lots was evaluated after storage under accelerated conditions.

Comparability data indicate that total protein content, estimated spike protein (rS) content and potency of both lots used in the phase 3 UK study are lower than in the lots used in the phase 3 US/Mexico study. These differences can at least partly be explained by the difference in formulation

strategy (total protein + 5% overage for UK study versus total rS protein, calculated by multiplying the active substance protein concentration and purity, for the US/Mexico study). As both clinical phase 3 studies showed similar results, these differences can be considered clinically qualified.

Comparability between finished product manufactured at PAR and SIIPL

The subsequent comparability study assessed comparability of the clinical lots manufactured at PAR with the SIIPL initial development scale lots, development/manufacturing scale PPQ lots and the commercial scale PPQ lots.

The SIIPL manufacturing processes at each scale of manufacturing are essentially the same with minimal differences. The assessment compares test results of release tests and additional characterisation tests, as well as a comparison of results of accelerated stability studies. The design of the comparability study is similar to that of the study between finished product manufactured at EBSI and PAR as described above.

Because of change of reference preparation and test method, comparability between the potencies of the clinical PAR finished product batches and the SIIPL batches could only be compared indirectly. This was performed in two different ways. Additional details can be found in the specification section below. All data indicate that the SIIPL lots have a higher potency than the PAR clinical lots, which is consistent with the comparability results at the level of the active substance. The increase in potency is not expected to impact clinical outcomes. This is supported by the results of phase 1 / 2 study 2019nCoV-101.

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 manufactured by PAR is comparable to finished product produced at SIIPL. The applicant is recommended to provide an updated analytical comparability report for finished product manufactured at PAR and SIIPL as additional characterisation and stability data become available **(Recommendation 29).**

Container closure system, microbiological attributes, compatibility

The container and closure system for Nuvaxovid finished product is Type I glass vials closed with bromobutyl rubber stoppers and an aluminium seal. The material of constructions of the vial and rubber stopper conform to pharmacopoeial standards. An extraction study has been performed. The applicant is recommended to further provide leachable studies for the finished product in vials and stoppers **(Recommendation 27).**

The vaccine is presented as a non-preserved product in a multi-dose vial. The applicant is proposing a 6 hour in-use shelf-life after the first puncture of the 10-dose vial, when stored between 2 to 25°C. Microbial growth studies presented showed no significant increase in growth for all test organisms during the first 24 hours at 2-8 °C and at 20-25 °C, indicating that the formulation does not support rapid microbial growth. However, conditions in clinical practice differ from the controlled conditions during in-use stability studies. Therefore, the SmPC indicates that from a microbiological point of view, after first needle puncture, the vaccine should be used immediately. If the vaccine is not used immediately, in-use storage times and conditions are the responsibility of the user.

A study conducted to evaluate the stability of the finished product in syringes shows that the finished product is chemically stable for at least 6 hours at both 2-8°C and 25°C when stored in a polypropylene syringe. The applicant is recommended to provide data of a supporting short-term stability study that includes both polypropylene and polycarbonate syringes under various potential extended in-use environmental conditions, such as hold temperature, agitation stress that may occur during transportation of syringes and indoor lighting **(Recommendation 28).**

Manufacture of the product and process controls

Finished product is manufactured, tested and released at the SIIPL Manjari site. Batch control testing will be performed by KBI Biopharma Leuven, Belgium, Bilthoven Biologicals B.V., Bilthoven, Netherlands and Novavax AB, Uppsala, Sweden. Batch release will be performed by Novavax CZ, Jevany, Czech Republic and Bilthoven Biologicals B.V., Bilthoven, Netherlands. Compliance with GMP has been appropriately documented for all sites.

In the initial application, the proposed commercial finished product manufacturing sites included the SIIPL Hadapsar facility and the SIIPL Manjari facility for the commercial process. Subsequently, the applicant indicated that the Hadapsar facility has not yet been established for commercial production. Consequently, commercial finished product production will only be performed at the Manjari facility.

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 is straightforward, i.e., preparation of the formulation buffer, thawing (if applicable) and pooling of the 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 and finishing. Vials are sterilised and depyrogenated in a tunnel at a minimum of 280 ºC for NLT 3 mins and the rubber stoppers in an autoclave at 122 ± 1 °C for 30 minutes.

All critical steps are adequately controlled. A number of in-process controls are proposed for the manufacturing process and these are considered satisfactory. The co-formulated bulk is an intermediate and is tested and released. The applicant is recommended to perform a bulk hold time study and to provide stability data for the intermediate hold time of not more than 24 hours **(Recommendation 31)**.

PPQ results are presented for batches consecutively manufactured at the Hadapsar facility and PPQ batches consecutively manufactured at the Manjari facility. Results are provided for critical process parameters, routine in-process controls, extended characterisation of the formulated bulk, batch homogeneity and batch analysis results. The PPQ studies confirm that the full scale commercial process performs effectively and is able to produce a finished product meeting its predetermined controls and acceptance criteria.

The applicant is recommended to submit the final process validation report for the commercial scale finished product manufacturing process at the Manjari premises once the results of the labelled lots (appearance, identity) are in place **(Recommendation 30)**. In addition, the applicant is recommended to provide a completed investigation of the increased endotoxin level in a specific PPQ batch **(Recommendation 32)**. This increased endotoxin level is close to the specification. As the specification is well below the *Ph. Eur*. endotoxin safety limit, there is no risk for the patient from this increased endotoxin level.

Product specification

The finished product specifications (add reference) includes general tests (appearance, pH, osmolality), protein concentration, identity (by western blot), potency (ELISA), content of Matrices A and C, safety tests (endotoxin, bioburden), extractable volume and container closure integrity (CCIT).

Since the rationale and justification for excluding specific quality attributes from the finished product specification was lacking in the application, a number of concerns were raised on the proposed specifications. No test is included for purity and the applicant is recommended to establishing a release

and shelf life purity specification for finished product **(Recommendation 33).** The absence of tests for subvisible particles, for the haemolytic activity of Matrix-A and Matrix-C, and for saponin integrity have been properly justified. Polysorbate 80 concentration cannot be measured in the finished product for release or stability because of interference in the assay by oleic acid residues originating from the adjuvant. The applicant is recommended to include dynamic light scattering to control the particle size distribution of the finished product, which is mainly determined by the Matrix–A and Matrix–C complexes of the adjuvant **(Recommendation 38).** The applicant is also recommended to established a two-sided specification for osmolality and to re-evaluate the total protein specification limits once 30 finished product batches have been manufactured **(Recommendations 23 and 34).** Furthermore, the applicant is recommended to perform the container closure integrity test as described in the US Pharmacopoeia (**Recommendation 35**).

The initially proposed lower acceptance criterion for potency was based on the release potency of a clinical batch that was recalculated to the current reference preparation. Because of change of reference preparation and test method, a direct comparison of finished product potencies could not be made. Instead, a conversion factor was used. The recalculation factor could not be accepted as it was based on the Gen1v1 potency assay, which was abandoned because of too high potency readouts and replaced with the Gen1v2 potency assay. A major objection was raised requesting an adequate bridging between the two reference preparations to be able to rely on data generated with the old potency assay and reference preparation. In response to the major objection, the applicant increased the lower limit for the finished product potency based on the measured Gen1v2 potency values for the active substance used to manufacture finished product for the US/Mexico Phase 3 study. This approach removes the reliance on the conversion factor and is considered acceptable. The adjusted lower limit is considered justified. Nevertheless, it is still considered essential that the applicant calibrates the old and the new reference standard against each other in the Gen1v2 potency assay in the presence of Matrix-M1. Once bridged, the finished product release and shelf-life acceptance criteria of the potency assay should be reviewed and updated as appropriate. This data is considered necessary to firmly link the potencies of finished product batches used in clinical phase 3 studies and commercial batches and ensure consistent product quality. It is therefore requested as a Specific Obligation (**Specific Obligation 2)**.

No new impurities / degradation products are formed during the finished product manufacturing process.

The applicant has provided a nitrosamine risk evaluation in line with EMA/369136/2020 and EMA Questions and Answers document EMA/409815/2020 for the finished product. Currently identified potential sources of nitrosamines impurities have been adequately addressed by the applicant, supporting the conclusion that there is no identified risk or the presence of nitrosamine impurities in Nuvaxovid finished product.

Analytical methods

For compendial methods, appropriate reference is made to the *Ph. Eur*. Non-compendial methods are described in sufficient detail. Validation reports were provided for western blotting, potency by ELISA (both Gen1v1 as Gen1v2), Matrix A and Matrix C content by RP-HPLC-UV and qualification reports for the compendial sterility and endotoxin tests, and total protein concentration by CBQCA (3-(4-carboxybenzoyl)quinoline-2-carboxaldehyde). A validation report for the CQQCA method remains to be submitted (**Recommendation 37**).

Batch analysis

Batch analysis results are provided for three batches manufactured at the Hadapsar premises, three PPQ batches manufactured at the Hadapsar Premises, and three commercial scale PPQ batches

manufactured at the Manjari premises according to the commercial process. Batch analysis results comply with the specification and confirm acceptable consistency. Some variability in relation to potency was observed.

Reference materials

The SARS-CoV rS reference standard is used as comparator in the western blot analysis, and as reference standard in the total protein analysis by CBQCA, and relative potency assay by ELISA. The reference standard is prepared from an active substance batch. It's preparation and calibration are suitably described (please refer to the active substance section). For the quantitative finished product assays the reference standard is mixed with Matrix-M to mimic the finished product formulation. This approach is acceptable. As discussed above as part of a specific obligation the applicant should calibrate the potencies of both reference standards against each other in the Gen1v2 finished product assay.

Stability of the product

The proposed shelf-life for the finished product is 9 months at 2-8°C.

This is supported by long term stability studies for 10 months of a PAR clinical batch, 9 months of a PAR clinical batch, 3 months of stability data for three PPQ batches manufactured at SIIPL and one month of stability data for three commercial-scale PPQ batches manufactured at SIIPL. Data from PAR can be considered as representative of commercial product since comparability to the SIIPL lots has been demonstrated.

In addition, accelerated studies (25 ± 2°C) were performed the above mentioned batches and stress studies (40 ± 2°C) for the PAR clinical batches. Both clinical PAR batches were stored in upright and inverted position and the SIIPL batches in inverted position only. This is acceptable as the inverted position can be considered worst-case.

The clinical PAR lots were tested for appearance, pH, osmolality, sterility, potency by ELISA, protein concentration, identity, Matrix A and Matrix C concentration, cholesterol concentration, phosphatidylcholine concentration, saponin integrity and particle size. Commercial lots were tested against the stability specification (appearance, pH, osmolality, sterility, container closure integrity, relative potency, protein concentration, identity). The testing panels include appropriate stability-indicating methods. In addition, results of characterisation tests are provided for commercial lots. Testing frequency is appropriate.

Clinical batches manufactured at PAR met all specifications up to 10 months, at long term conditions (2°C to 8°C). A downward trend in potency is observed, which is not statistically significant. Furthermore, for one clinical batch the protein concentration results at 5, 6, 9 and 10 months are part of an ongoing out of trend investigation. This is also the case for another clinical batch at 6, 7, 8 and 9 months. The investigation is still ongoing. The applicant confirmed that the out of trend of protein concentration is method related and not product related and this is considered acceptable. The applicant is nevertheless recommended to provide the full investigation report of the atypical low protein concentration results **(Recommendation 40)**.

The degradation rates for PAR and SIIPL did not show statistically significant differences for the critical quality attributes (pH, osmolality, identity, total protein concentration and potency). The applicant is recommended to update the statistical analysis of long-term stability results as additional data becomes available for on-going stability studies for SIIPL and PAR finished product lots

(Recommendation 41). The applicant is also recommended to provide a separate stability protocol to describe the post-authorisation stability program **(Recommendation 39).**

A photostability study was performed according to ICH Q1B using finished product manufactured by PAR. It can be concluded that the product should be stored in the original carton in order to protect from light. However, results show that short term (24 and 72 hours) exposure to visible light is not detrimental to product quality. 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 (**Specific Obligation 1).**

Adventitious agents

The Nuvaxovid manufacturing process incorporates control measures to prevent contamination and maintain microbial control. These controls include appropriate sourcing, testing and control of raw materials, cell and virus banks and in process materials.

Each material is assessed for the risks related to the following adventitious agents as appropriate:

- Microbial contaminants including bacteria, fungi, and mycoplasma/spiroplasma
- Viral contaminants including endogenous and adventitious viral agents
- Transmissible spongiform encephalopathy/bovine spongiform encephalopathy agents (TSE/BSE) according to the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) guideline, Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products (EMA/410/01 Rev. 3).

Controls to ensure freedom from contamination with adventitious agents include:

- Use of non-animal derived components and raw materials wherever possible
- Verification of the source and origin of components and raw materials (e.g. geographic, chemical, biological)
- Testing of virus stocks, virus banks, and cell banks for relevant microbial and viral contaminants
- Testing of production harvests for the presence of adventitious agents including microbial (including mycoplasma/spiroplasma) and viral agents
- Incorporation of steps in the manufacturing process demonstrated to remove/inactivate potential viral contaminants
- Evaluation of the raw materials and primary packaging materials for their risk of BSE/TSE contamination.
- Process controls (e.g. limits on processing time, filtration of buffers and in process solutions, monitoring of bioburden and endotoxin) designed to reduce and control bioburden and endotoxin contamination in the process.

A clear tabulated overview of the raw materials of biological origin used in the production process is provided, indicating the stage of manufacture used, source/origin, the risk evaluation performed, and certification of origin (as applicable).

Non-viral adventitious agents

An adequate control strategy for the control of potential microbial contaminants including bacteria, fungi and mycoplasma/spiroplasma has been developed. This covers starting materials (cell banks, virus stocks), raw materials, process controls, and product specifications. Together with an appropriate

GMP adherence (conformed by GMP inspection outcome) microbial quality of the finished product is sufficiently assured.

Based on the presented information, it is agreed that the risk of BSE/TSE contamination of finished product is considered negligible.

Viral adventitious agents

An adequate control strategy has been developed for the control of potential adventitious (viral) agents' contamination. This comprises starting materials (cell banks), virus stocks, process controls, and product specifications. Sf-Rhabdovirus sequences were identified in the WCB by RT-PCR and confirmed by MPS-Seq datasets. In addition, low-level positive PCR result for Sf-Rhabdovirus in active substance lots were detected, at or below the level of sensitivity of the assays. This can be expected because most Sf9 cell lines are contaminated by Sf-rhabdovirus and this is not considered to be a concern. Satisfactory clearance of Rhabdovirus was demonstrated in the viral clearance studies. Sf9 cells are known to contain nucleotide sequences that code for reverse transcriptase (RT). Of note, the characterisation of the cell banks to date includes a number of studies that were performed to demonstrate that the cell banks are free of infectious retrovirus. According to the applicant, despite the fact that RT equivalent to ~$1x10^3$ RVLP was detected, there is a low risk of the presence of infectious virus for two reasons: the NGS assay was validated and no retrovirus sequences were detected in harvest material and the active substance purification process has been proven to offer at least 13.99 LRV for a model retrovirus (see below viral clearance studies). RT activity detected at levels below the sensitivity of the assay could be expected as the test item is manufactured from Sf9 cells and the very low level is likely due to non-infectious retrotransposon elements within the Sf9 genome.

Viral clearance studies

Based on the information on the raw materials of biological origin used in the production process which have a potential to harbour viral contaminants, a robust strategy for virus clearance is needed.

Convincing viral clearance studies were performed in accordance with ICH Q5A.

The choice of the identified process steps for virus clearance are considered appropriate.

The selection of the model/relevant viruses used in the viral clearance studies are sufficiently justified. Adequate interference, matrix effects and cytotoxicity studies were performed. The lowest dilution that could be evaluated without significant cytotoxicity or viral interference was assessed.

Sufficient information is provided in support of the scale down model, process parameters and study design. Process parameters reflect (worst-case) routine large scale production conditions.

Based on the totality of evidence, it is agreed that the risk of viral contamination in Nuvaxovid is low with a sufficient safety margin as regards the risk of (infectious) viral contaminants present in the finished product.

Post-approval change management protocol

The applicant included a Post-Approval Change Management Protocol (PACMP) to support addition of active substance manufacturing and testing sites to supplement commercial demand.

The protocol outlines the information to be submitted to request approval for future active substance manufacturing sites, to supplement manufacture by the currently approved site SIIPL. Future sites will have GMP and MIA certification in place with an appropriate inspection record.

The PACMP defines the required elements to demonstrate overall comparability between the approved site and additional sites to achieve consistency and control of the active substance manufacturing process and product at the new site in comparison to the approved site. A dual approach is implemented to evaluate (1) the active substance manufacturing process via process comparability (i.e. process validation) and (2) active substance product via analytical comparability. The active substance manufacturing process at the new facility will be compared to the active substance manufacturing process at the approved site (SIIPL) to define any potential differences and appropriate mitigation, as applicable. The initial marketing authorisation application included data to demonstrate analytical comparability of the active substance produced at SIIPL to material manufactured at FDBU, where pre-PPQ material at FDBU was used to formulate finished product for Phase 3 trials. The active substance at the new facility will be evaluated against the active substance from SIIPL to ensure that the biochemical (purity), biophysical (structural), and biological (potency) properties of the final active substance at the new facility is comparable. As requested, 3-way comparability for the active substance will be performed, comparing the active substance from the new facility to material both from SIIPL and the clinical manufacturing site FDBU. Upon request during the procedure, the PAMCP was revised and considered generally in line with the EMA Q&A on post-approval change management protocols (EMA/CHMP/CVMP/QWP/586330/2010).

In the initial application three additional PACMPs were included. These related to an additional finished product and adjuvant manufacturing and testing sites and to an alternate finished product formulation process. Further to concerns raised during the procedure these PACMPs have been withdrawn by the applicant.

2.4.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

Quality data to support consistent quality of Nuvaxovid are considered sufficient in the context of a conditional Marketing Authorisation in the current (COVID-19) pandemic emergency situation. Having considered the emergency situation and the quality documentation provided, the CHMP imposed two specific obligations (SOBs) with clearly defined due dates (refer to Conclusions for details). It is expected that the applicant will be able to provide the requested data and thereby fulfil the specific obligations. Based on the applicant's plans and documentation, it is expected that data to fulfil the SOs will be submitted between February 2022 and end of January 2023.

During the procedure, two major objections were raised, in relation to the control of purity and potency. Additional data have been submitted by the applicant during the procedure in response to the major objections and other concerns raised. Further information is provided below on the resolution of the major objections and the rationale for accepting some open issues to be addressed as Specific Obligations post-marketing. Several other issues, 46 in total, are further highlighted as Recommendations (RECs) to be addressed by the applicant post-authorisation. These cover various aspects of the active substance, finished product and adjuvant and are detailed in Annex I to this report.

An exemption from Article 51 of Directive 2001/83/EC was sought regarding potency testing of the finished product at Serum Institute of India Pvt. Ltd. (SIIPL), 212/2, Off Soli Poonawalla Road, Hadapsar, Pune - 411028, Maharashtra, India. Finished product EU-release potency testing will be performed at SIIPL until 31st March 2022. From this date onwards, potency testing will be performed by a site located in the EU (either the currently approved release testing site KBI Biopharma, Technologielaan 8, B-3001 Leuven, Belgium or an additional site which is intended to be added via variation post-approval (Novavax CZ a.s. Bohumil 138, 281 63 Jevany, Czechia)). Having considered

the ongoing COVID-19 epidemiological situation, the duration of the derogation and that it is acceptable from a quality point of view, this approach was accepted and reflected accordingly in the terms of the Marketing Authorisation (Annex II, Section A of the Product Information).

Active Substance

During the procedure, a number of issues were raised concerning the process development, demonstration of comparability and control of purity. The main points are summarised below.

Overall, comparability data provided for the full-scale lots active substance and finished product manufactured at the proposed commercial manufacturing site (SIIPL) Support a conclusion that the commercial product manufactured at SIIPL will be comparable to clinical material. However, the SIIPL active substance cannot be considered to be fully comparable as regards potency (i.e. higher in commercial batches versus clinical batches), binding kinetics and purity when compared to the materials used in the clinical studies. These differences can be justified as they are not expected to have an adverse impact on safety or efficacy profiles. This is 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 still considered acceptable. In this respect, it should be noted that the upper limit for protein content is significantly lower than the 25 µg/0.5 mL dose used in phase 1/2 study material.

For release, purity is assessed by SDS-PAGE combined with densitometric scanning. No other methods for the estimation of purity and impurities are in place. During the procedure a major objection was raised in relation to limitations of the proposed control of purity and the applicant was asked to provide further evidence that SDS-PAGE with densitometric scanning is a sufficiently quantitative and accurate method to control purity. In addition, the applicant was asked to further justify the proposed specification limit and to develop additional methods for control of purity. In response, the applicant provided additional data and justifications to support the SDS-PAGE method suitability and proposed acceptance limit. Based on the responses provided, the proposed control of purity using the SDS-PAGE method is acceptable, considering that an acceptable safety profile has been shown for the FDBU batches tested in clinical studies and that these batches are considered worst-case with respect to impurity levels, compared to commercial batches. The major objection raised was therefore considered adequately resolved. Several commitments have also been made by the applicant to further improve the control of purity and impurities.

A PACMP has been included covering future additions of active substance manufacturing sites, to supplement manufacture by the currently approved site SIIPL. As requested, future comparability exercises for the active substance will include a 3-way comparison, where active substance from the new facility will be compared to material both from SIIPL and from the clinical manufacturing site FDBU.

Finished product

The finished product is a sterile, preservative-free, aqueous buffered dispersion for injection containing the SARS-CoV-2 rS protein as active substance. The active substance is co-formulated with Matrix-M1 adjuvant and presented in a multi-dose vial containing ten doses of 0.5 mL.

The potency of the finished product batches used in clinical studies is currently not considered to be fully linked to the potency of the commercially manufactured batches at SIIPL, raising uncertainty in comparing the potency of commercial finished product batches with those of clinical batches and defining clinically qualified potency limits based on batches used in clinical phase 3 trials. A major objection was therefore raised during the procedure requesting an adequate bridging between the reference preparations used to be able to rely on data generated for the clinical material, using previous versions

of both potency assay and reference preparation. Based on the clarifications provided by the applicant, it can be concluded that the batches manufactured at SIIPL are at least as potent as the least potent batch used in clinical studies. In addition, the lower limit for the product potency specification was increased, which is considered a conservative approach. However, to further support this conclusion, as a Specific Obligation, the applicant should bridge the relevant reference standard lots (i.e. calibrate reference standards against each other in the Gen1v2 finished product assay in the presence of Matrix-M1) to firmly link the potencies of finished product batches used in clinical phase 3 studies to those of commercial batches. Once the references standards are adequately bridged, the finished product release and shelf-life acceptance criteria of the potency assay should be reviewed and updated as appropriate **(specific obligation)**.

The proposed specifications, as demonstrated by the submitted data, are suitable to control product quality. Due to the rapid development, real time stability data for finished product are limited but data from clinical batches are considered representative to support the shelf life of the finished product. As a specific obligation the applicant will provide additional stability data on commercial batches to further support the shelf life of the product over the entire storage period **(specific obligation)**.

2.4.5. Conclusions on chemical, pharmaceutical and biological aspects

The data presented to support consistent quality of the medicinal product Nuvaxovid are considered to be sufficient in the context of a conditional marketing authorisation in the current (COVID-19) pandemic emergency situation. The CHMP has identified specific obligations to address remaining uncertainty in relation to quality issues that may have a potential impact on the safe and effective use of the medicinal product, and which therefore are needed to achieve comprehensive pharmaceutical (quality) data and controls for the product. The specific points that need to be addressed in order to fulfil the imposed specific obligations are detailed below.

SOB 1: In order to ensure consistent product quality during shelf life, the MAH should provide additional information on stability of the finished product.

The MAH should provide additional finished product stability data to confirm the long-term storage period of the finished product manufactured at the Serum Institute of India Pvt. Ltd. (SIIPL). Stability studies updates, including results of characterisation tests, should be provided post-authorisation for three PPQ lots manufactured at SIIPL using the specified manufacturing process and three PPQ lots manufactured at SIIPL using the commercial scale manufacturing process, upon availability of data for 3, 6, 9 and 12 months and completion of the study. Due date: 31 January 2023 with interim, monthly updates beginning February 2022.

SOB 2: 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.

The MAH should bridge reference standard lots (intermediate reference standard and previous reference standard) and the Primary Reference Standard in the SARS-Cov-2 rS binding ELISA Generation 1 Version 2 potency assay in the presence of Matrix-M1 adjuvant, to firmly link the potencies of finished product batches used in clinical phase 3 studies to those of commercial batches. Once bridged, the finished product release and shelf-life acceptance criteria of the potency assay should be reviewed and updated as appropriate. Due date: 31 July 2022

2.4.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress,

the CHMP recommends additional points for investigation, as listed in Annex I of this document.

2.5. Non-clinical aspects

2.5.1. Introduction

The non-clinical program was conducted in consideration of the appropriate regulatory guidelines for vaccine development. SARSCoV-2 rS with Matrix-M1 adjuvant vaccine-induced cellular and humoral immune response were assessed across multiple species, including rodents and NHPs. Live virus challenge studies were performed in mice, hamsters, cynomolgus macaques, and rhesus macaques. A standard toxicology program to support vaccine development has been undertaken for SARSCoV-2 rS with Matrix-M1 adjuvant.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

A number of animal species have been used to test the immune response, i.e. mice, baboons, hamsters, cynomolgus monkeys and rhesus macaques

Mice

Studies in mice (BALB/c) have been conducted to optimise the protein construct based upon the confirmation of the protein and the involvement of an adjuvant. Five studies have been conducted in BALB/c mice.

The first study in mice has been conducted to evaluate the following constructs: BV2365 "3Q" comprising a full-length S protein with amino acid substitutions in the S1/S2 cleavage domain and furin cleavage site introduced to confer protease resistance; BV2369, "3Q-ΔFP806-815" construct with deletions in the hydrophobic fusion peptide; and a receptor binding domain (RBD) construct received from Scripps Research Institute (La Jolla, California) representing the intact receptor binding domain of the SARS-CoV2 S protein only. This study has indicated that the mutations 3Q and 3Q-ΔFP806-815 introduced in the S protein are insufficient in increasing the immunogenicity of the product. In this prime-boost regimen study it emerged that the adjuvant/antigen combinations provided better immunogenicity and better protection than the non-adjuvanted antigens. In addition, the Matrix-M1 adjuvant had a dose-sparing effect, with similar immunogenicity seen for 1 and 10 ug antigen adjuvanted with 5 ug Matrix-M1. The enhancing effects of Matrix-M1 adjuvant on antibody production were expected based on the applicant previous experience with the Matrix-M1 adjuvant from other vaccine programmes (MERS and Ebolavirus), as well as the scientific literature (saponin-based adjuvants, so called ISCOM or immune-stimulating complex adjuvants, have been used in a large number of vaccine development programmes over the last approx. 40 years).

In a second study in BALB/c mice three different constructs have been tested with small mutations in the spike protein to enhance stability and immunogenicity in the presence of Matrix M1 adjuvant. BV2365 and BV2373 were similarly immunogenic by all serology assays performed (anti-S IgG ELISA, hACE2 receptor binding blocking ELISA and neutralisation of SARS-CoV-2 virus in vitro), while BV2369 was immunogenic as measured by anti-S IgG ELISA but did not induce functional antibodies able to block the spike-ACE2 interaction and neutralise SARS-CoV-2 in vitro. For this latter reason BV2369 was excluded at this stage. The remaining 2 lead antigens (BV2365 and BV2373 ie SARS-CoV-2 rS) were

tested for protective effect against SARS-CoV-2 challenge, at 10 ug level, with or without 5 ug Matrix-M1 adjuvant, in a prime-boost regime. These 2 antigens gave similar protection against challenge with SARS-CoV-2 strain. The 2 lead antigens were tested for protective effect against SARS-CoV-2 challenge, at 10 µg level, with or without 5 ug Matrix-M1 adjuvant, in a prime-boost regime in mice sensitised for SARS-CoV-2 by intranasal instillation of adenovirus vector expressing human ACE2. It was shown that both constructs protect against the bodyweight loss induced by challenging the mice with SARS-CoV2 virus. One of the most sensitive markers for disease appeared to be the body weight which was daily measured as recommended in the WHO Guideline 2014. The effects on body weight loss clearly showed the protective effect of the vaccine, being more effective after two dosages. The more stable 3Q-2P BV2373 construct was chosen to be further developed. In addition, it was shown in this study that adjuvant/antigen combinations provided better immunogenicity and better protection than the non-adjuvanted antigens and that the Matrix-M1 adjuvant was dose-sparing.

A third study also tested the SARS-CoV-2 viral challenge in mice pre-treated with an adenovector expressing the hACE2 receptor. The effects on body weight loss clearly showed the protective effect of the vaccine, being more effective after two dosages. Immunogenicity was maximal and protection fully achieved with 10 ug adjuvanted antigen dose, and 1 ug adjuvanted antigen was similarly effective. Furthermore, the vaccination strongly induced adequately levels of functional antibodies against the SARS-CoV2 spike protein as well as the binding to the hACE2 Receptor. Of note, animals with low and suboptimal responses did not show vaccine-associated enhancement of pulmonary pathology.

The fourth study in Balb/c mice indicated the importance of the adjuvant Matrix M1 in increasing the response to SARS-Cov2 spike protein, including stimulation of the cellular immunity. Biomarkers of the cellular immunity such as interferon-gamma as well as germinal centre B cells are strongly increased by the vaccine-antigen with Matrix M1. This involvement of cellular immunity is important in relation to the duration of the immune response. Based on ELISpot and flow cytometry, the antigen-specific recall response after immunisation with 10 µg non-adjuvanted antigen was dominated by Th2 cells; in contrast, the antigen-specific recall response after immunisation with 10 µg antigen adjuvanted with 5 µg Matrix-M1 was more directed towards Th1.

In the fifth study, the applicant compared the Matrix-M1 with Alum as an adjuvant. The Matrix-M1 adjuvant induced a higher immunogenicity with functional antibodies as compared with the Alum adjuvant.

On the basis of the studies carried out in mice it was concluded that the 3Q-2P protein is able to induce an appropriate immune response, which is significantly enhanced by the Matrix-M1 adjuvant. The immune response was not only limited to antibody responses but included also an adequate response in cell-mediated immunity which was Th1-biased. The immune response is dependent on the dose of the antigen rS (3Q-2P protein) in an optimal ration compared to the adjuvant. This ratio might be different in various species as the ratio in NHP is around 1 vs. 10, while in rodents it might be higher 1 vs. 2 or less. The data also showed that the immune response protect against the morbidity of the challenge, e.g. loss of body weight.

The applicant submitted studies to evaluate the mode-of-action of the adjuvant Matrix-M1. These studies have been conducted in BALB/c mice, and one *in vitro* study has been included. The *in vitro* study suggests a mechanism of action of Matrix-M1 which is related to active lysosomal processing, indicating that the mode of action of saponins is not related to saponification as such. Accordingly, saponins induced specific cellular mechanisms. A study with Ebola Glycoprotein clearly showed that the effect of Matrix-M1 was local. Spatial and large temporal separation of the administration of the adjuvant from the protein clearly reduced the adjuvant action. Administration in the same area within a time-slot of 48 hours is crucial in this respect. Cytokines were produced transiently with a peak

within 24 hours from administration, with the increase in cytokines preceding the increase in antibody response.

Studies in other species

Hamsters are susceptible preclinical model for SARS-CoV-2 infection. Following challenge, mild to moderate, transient disease comprising body weight loss, respiratory signs and lethargy is seen, as well as pneumonia associated with virus replication in upper airways and lung (Muñoz-Fontela et al. Nature. 2020 586(7830):509-515).

The study in hamsters supports the choice of the antigen in the vaccine, and the added value of the use of Matrix-M as an adjuvant. This antigen/adjuvant combination induced a strong protective immunogenic response, and a second dose enhanced further the immune response. The administration of the antigen/adjuvant combination also strongly reduced viral replication as shown by a reduced level of genomic as well as sub-genomic viral RNA in oral swabs. Protection from disease was shown by reduced body weight loss and lethargy as well as reduced lung pathology. There was no evidence of vaccine-enhanced disease.

A study in middle aged (10-16 years old) baboons was designed to study the functional immunogenicity by measuring the binding of IgGs to the spike protein and to the hACE2 receptor by ELISA. The adjuvant enhanced the immune response towards Th1, including activity of CD4+ T cells. 1 and 10 µg adjuvanted antigen induced similar humoral and functional responses, with 0.1 and 0.01 µg antigen levels being sub-optimal (5 µg Matrix-M1 for all antigen doses). A booster injection given after a period of 3 weeks, enhanced further the immunogenicity as measured by anti-S IgGs, functional antibodies against hACE2 receptor, as well as cellular immunity. Total duration of the study is 245 days. Immunogenicity against SARS-CoV2 was optimal around day 28-35 after the booster. Afterwards it decreased at day 120 and further at day 182, but less when using the adjuvant.

In another pivotal study, cynomolgus monkeys were immunised with full human dose (5 µg), or higher antigen dose (25 µg) with the same dose of Matrix-M1 adjuvant (50 µg). Binding as well as functional antibody responses were induced after the first immunisation, and protection against lung pathology after SARS-CoV-2 challenge was also seen already after the first immunisation, indicating that some protection against disease may be present already after a single immunisation with the vaccine. Nevertheless, binding as well as functional antibody responses increased markedly after the second immunisation, supporting the 21 day interval prime/boost vaccination regimen used in humans. Furthermore, in the vaccinated animals the viral replication of SARS-CoV2 was reduced in upper and lower respiratory tract. No evidence of VAERD following exposure to SARS-CoV-2 virus was seen, even in animals which had received suboptimal vaccination regimens.

A pivotal study in rhesus macaques has applied the full human dose of 5 µg SARS-CoV-2 rS antigen and 50 µg Matrix M1 adjuvant. Immunisation with one dose resulted in partial protection against viral replication in airways. Providing a second dose resulted in nearly complete protection. All SARS-CoV-2 rS with Matrix-M1 adjuvant vaccination doses and regimens used in this study were immunogenic in rhesus macaques, with the two-dose regimens resulting in the greatest immunogenicity and protection against SARS-CoV-2 challenge that was comparable between both the 5 and 25 µg antigen dose levels. IgA response was generated in this animal model.

From the studies in hamsters, cynomolgus macaques and rhesus monkeys, it emerged that vaccination with the BV2373 construct in combination with the adjuvant Matrix-M1 leads to a robust immune response that is proven to be effective against the disease symptoms of SARS-CoV-2 infection and in reducing viral replication.

In a second study in Rhesus monkeys two doses (full human dose) of 5 µg SARS-CoV-2 rS with 50 µg Matrix-M1 adjuvant was well tolerated. The final report will show the results on a challenge with SARS-CoV-2 virus after 6 or 12 months and provide information on the duration of protection.

2.5.2.2. Secondary pharmacodynamic studies

No studies on the secondary pharmacodynamics have been performed, which is in accordance with applicable guidelines.

2.5.2.3. Safety pharmacology programme

Safety pharmacology studies were not conducted with SARS-CoV-2 rS with Matrix-M1 adjuvant vaccine, which is in line with the recommendation of the WHO Guidelines on Non-clinical Evaluation of Vaccines (2005), also given the availability of supporting non-clinical and clinical data, which indicated that the vaccine did not affect physiological functions other than those of the immune system. The repeat-dose toxicity study included daily clinical observations, a complete panel of haematology, clinical chemistry, and coagulation evaluations, as well as histopathology evaluation on a full panel of tissues. There was no evidence of toxicity on physiological functions (e.g., central nervous system, cardiovascular, respiratory, or renal functions) based on these evaluations. In addition, multiple repeat-dose toxicity studies have been conducted in rats and rabbits with the Matrix-M1 adjuvant and viral glycoproteins produced in the baculovirus/Sf9 platform with no evidence of overt systemic or organ-specific toxicities identified.

2.5.2.4. Pharmacodynamic drug interactions

No studies on pharmacodynamic drug interactions have been performed, which is in accordance with applicable guidelines.

2.5.3. Pharmacokinetics

WHO guidelines on non-clinical evaluation of vaccines (WHO 2005) and vaccine adjuvants and adjuvanted vaccines (WHO 2013), traditional absorption, distribution, metabolism, and excretion (ADME) evaluations are not generally needed for vaccines. The safety concerns associated with vaccines are generally not related to the pharmacokinetics but are related to the potential induction of immune response.

2.5.4. Toxicology

The non-clinical toxicology program was designed to support development of the SARS-CoV-2 rS vaccine with Matrix-M1 adjuvant and a set of GLP compliant studies was submitted by the applicant. A repeat-dose GLP-compliant study with SARS-CoV-2 rS in rabbits was performed, with or without the adjuvant Matrix-M1. In addition, 6 GLP-compliant repeated dose toxicity studies in rats and rabbits with other vaccines in combination with Matrix-M1, or Matrix-M1 alone, were provided, in which the toxicity of Matrix-M1 was evaluated.

2.5.4.1. Single dose toxicity

No single dose toxicity studies were performed by the applicant, which was agreed.

2.5.4.2. Repeat dose toxicity

In the repeated dose toxicity study with SARS-CoV-2 rS in New Zealand White rabbits, animals received 4 intramuscular injections of SARS-CoV-2 rS with or without Matrix-M1. SARS-CoV-2 rS vaccine was administered on day 1, 8, 15, and 36 and induced high anti-S IgG titers. Addition of Matrix-M1 adjuvant significantly enhanced anti-S IgG responses. Vaccine administration affected clinical pathology parameters and histopathology, consistently with an immune stimulation following administration of a vaccine, including: minimally to mildly higher mean fibrinogen concentrations, moderately to markedly higher mean CRP and minimally higher mean globulin concentrations. These findings correlated with the microscopic observations of subacute inflammation at the injection sites. The vaccine-related findings were relatively mild and no changes were seen in parameters such as body temperature, food consumption or any of the haematological parameters. The observed effects resolved during the recovery interval, except for the injection site reactions. Addition of Matrix-M1 resulted in similar effects. Of note, the dosing schedule used was not in accordance with the proposed clinical schedule (the dose ratio of SARS-CoV-2 rS nanoparticle/Matrix-M1 used is different: 50/50 in the study vs 5/50 in the clinical situation).

The safety of Matrix-M1 was also evaluated in three studies in rabbits, either alone or in combination with other viral glycoproteins manufactured in the baculovirus-Sf9 system. In addition, three other studies (one in rabbits, two in rats) were submitted by the applicant in which the safety of Matrix-M1 was evaluated with or without a vaccine. Overall, consistent results were observed across these studies, and Matrix-M1 adjuvant was well-tolerated with no evidence of toxicity suggestive of any unusual risk or target organ toxicity. The findings were considered consistent with immune system stimulation consequent to administration of an active adjuvant, and comprised: local injection site inflammation, reversible enlargement of the lymph nodes draining the injection sites (but not elsewhere), and chemical markers of inflammation (i.e., CRP, fibrinogen, and globulin). Most of the findings were fully reversible after 3- to 4-week of recovery periods, although minimal to mild changes at the injection sites and in regional lymph nodes persisted in some animals.

2.5.4.3. Genotoxicity

The adjuvant Matrix-M1 was tested in a bacterial reverse mutation assay and an *in vitro* screening chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells. In both non-GLP assays, there was no indication for a genotoxic potential of Matrix-M1.

The confirmatory GLP-compliant bacterial reverse mutation assay and Mammalian Cell Micronucleus assay in CHO Cells with Matrix-M1 confirmed the absence of any indication for a genotoxic potential of Matrix-M1. Further in vivo studies were therefore not considered necessary.

2.5.4.4. Carcinogenicity

No carcinogenicity studies have been performed with the SARS-CoV-2 rS vaccine and Matrix-M1 adjuvant in accordance with the WHO Guidelines on Non-clinical Evaluation of Vaccines (2005) and Guidelines on the Non-clinical Evaluation of Vaccine Adjuvants and Adjuvanted Vaccines (2014).

2.5.4.5. Reproductive and developmental toxicity

A DART study in rats with SARS-CoV-2 rS + Matrix-M1 or Matrix- M1 alone (administered 27 and 13 days prior to cohabitation and on gestation day (GD) 7 and 15) has been performed. A non-GLP pilot study in rats indicated that SARS-CoV-2 rS adjuvanted with Matrix-M1 is immunogenic in female and male rats following one and two immunisations. In the DART study, 5 µg SARS-CoV-2 rS + 10 µg

Matrix-M1 or 10 µg Matrix- M1 alone were used, which are in given at a different ratio than in the clinically used dose (although the dose of SARS-CoV-2 rS is the same, the dose of Matrix-M1 is 5 times lower).

No male fertility studies were performed given no adverse observations in male reproductive organs were observed in the GLP repeat-dose toxicology study.

The DART study confirmed that SARS-CoV-2 rS + Matrix-M1 or Matrix-M1 does not affect reproductive or developmental parameters and no adverse findings on pregnancy/lactation, or development of the embryo/foetus and offspring through post-natal Day 21 were identified. (although some, incidental, not compound-related foetal observations were noted in all groups). Furthermore, administration of SARS-CoV-2 rS co-formulated with Matrix-M1 adjuvant induced high anti-S IgG titers in all vaccinated dams. Anti-S IgG antibodies were also found in F1 generation foetuses and pups (higher levels were observed in pups), confirming the transfer of maternal antibodies in postnatal stages of development, but also (although to a lesser extent) during the gestational period.

2.5.4.6. Local Tolerance

The absence of a dedicated local tolerance study for NVX-CoV2373 or Matrix-M1 Alone was endorsed. Local tolerance was evaluated as part of the repeat dose toxicology study in rabbits with SARS-CoV-2 rS Nanoparticle Vaccine with Matrix-M1 Adjuvant or Matrix-M1 Alone as well as in the cynomolgus, rhesus, and baboon NHP pharmacology studies.

Overall, administration of both the SARS-CoV-2 rS Nanoparticle Vaccine and the Matrix-M1 adjuvant proved to induce local irritancy and inflammation. These effects can be related to an immunological response towards the administered products at the injection site, which is a desired pharmacological mode of action of the vaccine and the adjuvant.

In the repeat dose toxicology study in rabbits, minimal to moderate subacute inflammation were found, which were generally similar between vaccine groups with and without Matrix-M1, and across all phases, and decreased in severity and incidence at the conclusion of the 3-week recovery period.

In the two supportive rabbit repeated dose toxicity studies, the injection site reactions were relatively mild after 3 or 4 injections, and after the 28-day recovery period only minimal injection site reactions persisted. In the supportive rat repeated dose toxicity studies, there were minimal to moderate local effects, including discolouration, inflammation and haemorrhage at the injection sites, which had markedly to fully decreased in severity after a 3-week recovery period.

Overall, the studies raise no concern regarding the local tolerance of either the SARS-CoV-2 rS Nanoparticle Vaccine or the Matrix-M1 adjuvant.

2.5.5. 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.

2.5.6. Discussion on non-clinical aspects

The rS antigen is being manufactured in baculoviral cells, which is not a mammalian cell culture, and therefore a different pattern of glycosylation is expected. The paucimannose pattern glycosylation induced by the insect cells has only limited effects on antibody binding and MHC molecule interactions of most predicted T-cell epitopes on the spike.

In general, the pharmacodynamic studies show that SARS-CoV-2 rS plus Matrix M1 induce an immune response in several species (mice, hamsters and monkeys) as shown by the induction of virus-neutralising antibodies, as well as by disrupting the binding to the hACE2 receptor. These studies showed also that the addition of Matrix-M1 is necessary to induce a sufficient immune response. Furthermore, it has been shown in a mouse model as well as in hamsters and monkeys that administration of SARS-CoV-2 rS plus Matrix M1 protects against SARS-COV2 infection, as shown by amelioration of body weight loss, protection from activity reduction, accelerated viral clearance, and protection against severe SARS-CoV-2-induced lung histopathological changes compared with placebo. Finally, data show the induction of a Th1 cellular immune response.

The nonhuman primate studies are still ongoing. Given the evolving landscape of the SARS-CoV-2 pandemic and emergent variant strains, as well as considering the global scarcity of non-human primates available for biomedical research, study designs for the two ongoing NHP studies (Studies 702-087 in baboons and 702-115 in rhesus macaques) have shifted to accommodate investigations into vaccines for SARS-CoV-2 variants of concern. Long-term data for protection against virus challenge in rhesus macaques will be reported after approval.

As the Matrix-M1 adjuvant is not currently marketed in a human vaccine in the EU market, Novavax is planning to conduct a biodistribution study in mice to evaluate the Matrix-M1 adjuvant, which may be of value in further understanding the mode of action of the adjuvant. Results of this study will be provided at a later stage. Challenges with the labelling of the Matrix-M1 adjuvant, prevented the study to be conducted earlier. Considering the extensive clinical package available at the time of initial marketing approval, the safety profile of the adjuvanted vaccine was considered acceptable without finalisation of the biodistribution study. Furthermore, the recruitment of immune cells, which might influence biodistribution, is mainly driven by the Matrix-M1 adjuvant (and not the vaccine antigen), as antigen and adjuvant are not bound. However, although the major influence to biodistribution is expected to be driven by the Matrix M1 adjuvant vs virus antigen, Matrix M1 adjuvant and antigen will be pre-mixed and, under these conditions, some interaction between Matrix-M1 adjuvant and the SARS-CoV-2 rS antigen is likely. The applicant therefore will include an additional study group with Matrix-M1 (labelled) + SARS-CoV-2 rS (unlabelled) in addition to the Matrix-M1 adjuvant (labelled) only group to assess the impact of antigen on the biodistribution of the adjuvant. This protocol of the biodistribution will indicate that an adequate dose will be supplied, and adequate tissues will be analysed at multiple timepoints, allowing to assess the absorption, distribution and clearance of the adjuvant.

Overall, the toxicology programme revealed no effects other than what expected when administering a vaccine. However, the doses used in both the repeated dose toxicity study in rabbits (50/50) and the DART study in rats (5/10) are not in line with the absolute human dose (5/50). In both studies, the ratio of antigen/adjuvant is different. In addition, in the DART study, the Matrix-M1 dose is 5 times lower than the clinical dose, whereas the Guidelines on the non-clinical evaluation of vaccine adjuvants and adjuvanted vaccines clearly indicates that 'the toxicity study should be performed using the highest anticipated human dose (in absolute terms) of the final adjuvanted vaccine'. In addition, the pharmacodynamic studies in various species have shown that the ratio of antigen/adjuvant may affect the immunogenic response, which indicates the relevance of the ratio vaccine/adjuvant for the pharmacological properties. According to the applicant, the antigen is not contained within the

saponin-bearing complex, nor are the antigen nanoparticles adsorbed to the Matrix-M1 adjuvant. However, in the intended drug product, Matrix-M1 adjuvant and SARS-CoV-2 rS (BV2373) antigen will be pre-mixed, and under these conditions, some interaction between Matrix-M1 adjuvant and the SARS-CoV-2 rS antigen are expected. Of note, in the mouse study aimed to investigate Temporal and Spatial Effects of Matrix-M1 Adjuvant Administration on Adaptive Immune Responses, with Recombinant Ebola Virus Glycoprotein it was found that separate administration of Matrix-M1 and antigen to the same i.m. injection site resulted in lower levels of antigen-specific antibodies compared to pre-mixed Matrix-M1 + antigen.

It is noted that in the repeated dose toxicity study with the SARS-CoV-2 rS vaccine, the majority of iliac lymph nodes (79%) was not assessed. According to the applicant this was due to the small size of these lymph nodes. The absence of enlarged lymph nodes implies that the missing lymph nodes were most likely normal and therefore the overall interpretation of the study can be accepted.

For the evaluation of reproduction toxicology, the applicant has used the rat as animal model. It is noted that placental transfer of antibodies in rabbits is more similar to humans compared to rodents. However, in the DART study, anti-SARS-CoV-2 rS spike IgG titers were measured in maternal, foetal, and pup serum samples. Titers measured in foetuses were approximately 8.0% of those present in dams, whereas nursing pups had anti-S lgG levels approximately 70-82 % of the IgG levels of the dams, indicating that sufficient antibody transfer occurred via placenta and especially lactation.

In addition, it is noted that In the DART study, the Matrix-M1 dose is 5 times lower than the absolute human dose. The administered dose was the maximum volume of clinical formulation (used for the early clinical studies) and, although the dose is smaller than the absolute dose that will be administered to humans, it does exceed the human dosage on a weight-adjusted basis by 40-fold. In addition, the final audited DART report includes data showing that the dose used in this study did induce an immune response. The study design and generated results are therefore considered acceptable.

2.5.7. Conclusion on the non-clinical aspects

No major non-clinical issues are identified in this application. Several concerns were identified and have been properly addressed by the applicant. The CHMP is of the view that non-clinical data reveal no special hazard for humans based on appropriate studies of repeat dose toxicity and reproductive and developmental toxicity.

2.6. Clinical aspects

2.6.1. Introduction

The applicant has submitted 4 clinical studies:

Study 2019nCoV-101 is a two part phase 1/2 randomised observer blinded study designed to evaluate the safety and immunogenicity of NVX-CoV2373, with part 1 as dose finding and part 2 as dose confirmation trial; Study 2019nCoV-501 Phase 2a/b, randomised, observer blinded placebo controlled study to evaluate the efficacy, immunogenicity and safety of NVX-CoV2373 in South African adult subjects living without HIV and safety and immunogenicity in adults living with HIV; two pivotal phase 3 trials, 2019nCoV-302 and 2019nCoV-301 randomised, observer blind, placebo-controlled trial to evaluate efficacy, safety and immunogenicity of NVX-CoV2373.

GCP aspects

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

For the pivotal trial 2019nCoV-302, an MHRA led GCP inspection was conducted for investigator sites and laboratories. There were no "Critical" findings identified during this inspection. There were 3 "Major" findings identified during this inspection relating to Sponsor Oversight, Laboratory Sample Management and Data Management. The organisations have provided corrective and preventative actions in response to the inspection report. These were reviewed by the GCP Inspectorate and are considered acceptable.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Tabular overview of clinical studies

Table 3. Clinical trials with SARS-CoV-2 rS with Matrix-M1 Adjuvant

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	Immunogenicity Safety	Dose 1/Dose 2 A: 150-300 (255) B: 150-300 (258) C: 150-300 (256) D: 150-300 (259)	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:	healthy adult participants ≥ 18 to < 85 years of age

			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		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)	122 M/137 F 57y (18-81) Group E: 121 M/ 134F 58y (18-84)	
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

2.6.2. Clinical pharmacology

Pharmacokinetics

No pharmacokinetics studies have been conducted for NVX-CoV2373. This is because pharmacokinetics studies are generally not needed for vaccines, consistently with current Guidelines on clinical evaluation of vaccines.

Pharmacodynamics

The pharmacodynamic profile of vaccines is defined by their immunogenicity, as detailed in the CHMP guideline "Guideline on Clinical Evaluation of New Vaccines" (EMEA/CHMP/VWP/164653/2005).

Mechanism of action

The SARS-CoV-2 rS vaccine with Matrix-M1 adjuvant (also referred to as NVX-CoV2373) is a protein nanoparticle vaccine (SARS-CoV-2 rS) constructed from the full-length, wild-type SARS-CoV-2 S glycoprotein (based on Wuhan-Hu-1 isolate), stabilised in its prefusion conformation administered with Matrix-M1 adjuvant, a saponin-based adjuvant derived from fractionated Quillaja saponins, phosphatidylcholine, and cholesterol. 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.

To date, there is no established correlate of protection for COVID-19.

Primary and Secondary pharmacology

The bioanalytical methods used to support the clinical development of NVX-CoV2373 were a micro-neutralisation (MN) assay to evaluate specific neutralising antibodies (nAbs) against SARS-CoV-2 in

human serum, an ELISA for the determination of specific IgG antibodies against S protein or N protein in human serum, an intracellular cytokine staining assay, and an hACE2 receptor inhibition assay to determine the inhibition titre in human serum for inhibiting the binding of SARS-CoV-2 S protein to the hACE2 receptor. The microneutralisation, anti-S protein binding IgG, and hACE2 receptor binding inhibition assays were all based on the original Wuhan strain.

All assays used to determine immunogenicity in the phase 3 studies were validated.

The following table provides an overview of the different SARS-CoV-2 PCR assays used in the clinical studies and their validation status.

	SARS-CoV-2 PCR Assay by clinical study				
	Phase 1 2019nCoV-101, Part 1	Phase 2 2019nCoV-101, Part 2	Phase 2 2019nCoV-501	Phase 3 2019nCoV-302	Phase 3 2019nCoV-301
SARS-CoV-2 PCR assay	**ThermoFisher TaqPath**	**ThermoFisher TaqPath**	**BD MAX**	**ThermoFisher TaqPath**	**Abbott RealTime SARS-CoV-2 Assay**
Validation status	Qualified	Qualified	Validated	Validated	Validated

Immunogenicity results

The immunogenicity data available so far were generated from study 2019nCoV-101 part 1 and 2, 2019nCoV-301, 2019nCoV-302, and 2019nCoV-501. Main findings are described below.

Dose finding studies: 2019nCoV-101 Part 1 and Part 2

Study 2019nCoV-101 is a two-part phase 1/2 randomised observer blinded study designed to evaluate the safety and immunogenicity of NVX-CoV2373. Part 1 is the first-in-human trial evaluating the safety and immunogenicity of SARS-CoV-2 rS with or without Matrix-M1 adjuvant in healthy adult participants 18 to 59 years of age at 2 sites in Australia. Part 2 commenced after positive results were observed following a formal analysis of the primary endpoints in Part 1 and was designed to evaluate the safety and immunogenicity of SARS-CoV-2 rS with Matrix-M1 adjuvant in healthy adult participants 18 to 84 years of age at multiple sites in the USA and Australia.

Both Part 1 and Part 2 evaluated 2 dose levels of SARS-CoV-2 rS (5 µg and 25 µg), which were based on the results of non-clinical studies with this antigen and on the results of clinical studies with other Novavax-based nanoparticle vaccines. Both parts also evaluated a single dose level of Matrix-M1 adjuvant (50 µg), based on previous clinical experience with Matrix-M1 adjuvant.

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 (see **Table** 4).

Table 4. Trial Design for Protocol 2019nCoV-101 (Part 1)

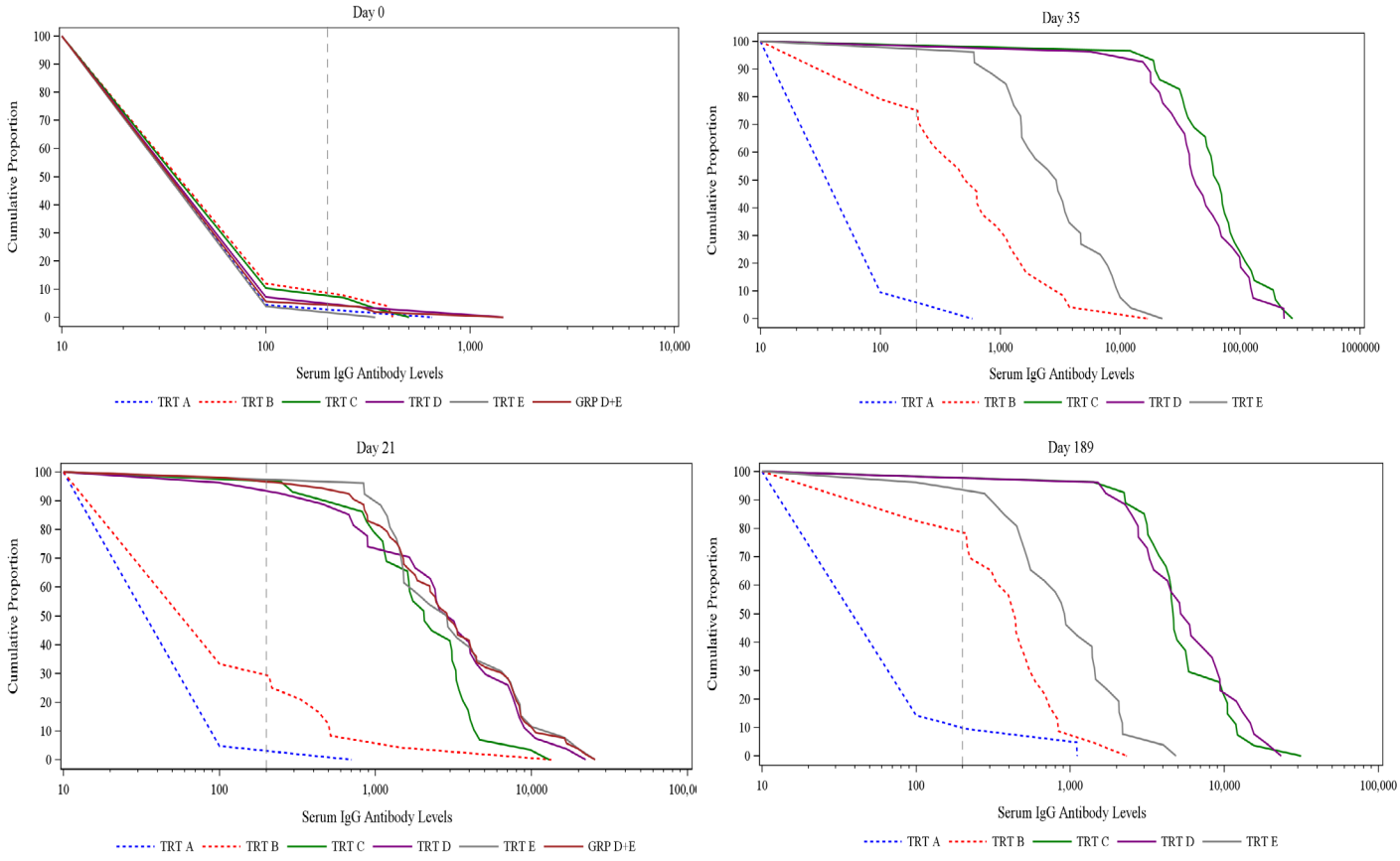
Trial Vaccine Group	Number of Participants		Day 0		Day 21 (+ 5 days)	
	Randomised	Sentinel	SARS-CoV-2 rS[1] (µg)	Matrix-M1 Adjuvant (µg)	SARS-CoV-2 rS[1] (µg)	Matrix-M1 Adjuvant (µg)
A	25	–	0	0	0	0
B	25	–	25	0	25	0
C	25	3	5	50	5	50
D	25	3	25	50	25	50
E	25	–	25	50	0	0

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.

Anti-S IgG was measured at Days 0 (baseline), 7, 21, 35, 49, 105, and 189 using a qualified IgG ELISA (Novavax Clinical Immunology, Gaithersburg, MD, USA). The Reverse Cumulative Distribution Curves showing the responses at D0, D21 (21 days post dose 1), D35 (14 days post dose 2) and D189 (6 months post dose 1) are presented below in Figure 6. Neutralising antibody responses showed a similar pattern.



Vaccine Group	TRT A	TRT B	TRT C	TRT D	TRT E
SARS-CoV-2 rS dose 1/2	0/0	25/25	5/5	25/25	25/0
Matrix-M1 Adjuvant dose 1/2	0/0	0/0	50/50	50/50	50/0

Figure 3 - Reverse Cumulative Distribution Function of Serum IgG Antibody Levels at Baseline and Following First Vaccination of SARS-CoV-2 rS with or without Matrix-M1 Adjuvant in Healthy Adult Participants 18 to 59 Years of Age (Per Protocol (PP) Analysis Set)

In conclusion, Part 1 showed that up to 2 doses of 5 µg and 25 µg SARS-CoV-2 rS with or without 50-µg Matrix-M1 adjuvant, administered 21 days apart, were immunogenic and well tolerated in healthy adult participants 18 to 59 years of age (see safety section for more details).

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

Table 5 Trial Design for Protocol 2019nCoV-101 Phase 2 (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.

Immunogenicity assessments comprised serum anti-S protein binding IgG, hACE2 receptor binding inhibition, neutralising antibodies, and cell-mediated immunity.

Neutralising antibody responses comparing the 18 to 59 years stratum and the 60 to 84 years stratum are shown below.

Table 6. Comparison of Neutralising Antibodies Specific for SARS-CoV-2 Wild-Type Virus Following Vaccination with SARS-CoV-2 rS and Matrix-M1 Adjuvant Regardless of Baseline Serostatus in Participants 18 to 59 Years of Age and 60 to 84 Years of Age (PP Analysis Set2019nCoV-101 Part 2)

Neutralizing Antibody Parameters	18 to 59 Years Stratum	60 to 84 Years Stratum
GMT at Day 0		
Group B (n = 24/27)	10.0	11.1
Group D (n = 23/26)	10.0	10.0
GMT at Day 21		
Group B (n = 8/13)	36.7	42.2
Group D (n = 11/10)	132.4	32.5
GMT at Day 35		
Group B (n = 23/26)	2200.8	980.5
Group D (n = 23/26)	1783.1	1034.2
SCR at Day 35		
Group B (n = 23/26)	96.2	100.0
Group D (n = 23/26)	96.2	96.2

Abbreviations: GMT = geometric mean titer; PP = Per-Protocol; SARS-CoV-2 rS = severe acute respiratory syndrome recombinant spike protein nanoparticle vaccine; SCR = seroconversion.

Note: Group B = 5/50 µg × 2; Group D = 25/50 µg × 2.
Source: T14.2.3.

Overall, it can be concluded that the interim results obtained in Part 2 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. The humoral immune response analyses by age subgroup show a potent response in both age groups, although the magnitude of the response was consistently lower in the older age stratum. The final clinical study report (CSR) should be made available as soon as possible to further evaluate the effect of age on the kinetics, amplitude or durability of vaccine-induced immune responses.

Main studies

2019nCoV-301

Study 2019nCoV-301 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 Nuvaxovid or placebo.

The main immunogenicity related endpoints were the analysis of antibodies binding to the SARS-CoV-2 S protein by ELISA, and SARS-CoV-2 neutralisation, both at Day 0 (baseline) and Day 35 (14 days after second study vaccination).

Demographics and baseline characteristics of participants in the PP-IMM Analysis Set were well balanced between the NVX-CoV2373 and placebo groups. Median age (range) was 65.0 years (18 to 95 years), with approximately 50% of participants ≥ 65 years of age. Approximately half the participants were male (50.1%), while the majority (79.1%) was White, not of Hispanic or Latino origin (80.7%), and located in the United States (93.0%). Black or African Americans (9.9%), American Indians or Alaska Natives (6.2%), and Asians (3.3%) were well represented. The majority of participants were overweight or obese (74.3%), with more than a third being obese (38.2%).

At 2 weeks following second vaccination (Day 35), serum IgG antibody geometric mean ELISA units (GMEUs) in the NVX-CoV2373 group were markedly increased relative to placebo across all age groups (48,918.0 vs 128.0, respectively, for participants ≥ 18 years of age; 63,890.4 vs 121.9 for participants 18 to < 65 years of age; and 37,594.3 vs 134.1 for participants ≥ 65 years of age) with no evidence of

placebo response. Serum anti-S IgG GMTs in the NVX-CoV2373 group were approximately 1.7-fold higher in the younger age cohort (18 to <65 years) than in the older age cohort (≥65 years). SCRs in the NVX-CoV2373 groups also were markedly increased relative to placebo across all age groups (97.3% vs 4.5% for participants ≥ 18 years of age; 98.0% vs 3.7% for participants 18 to < 65 years of age; and 96.6% vs 5.3% for participants ≥ 65 years of age).

Serum anti-S IgG levels at Day 35 in both serologically negative and serologically positive adult participants were increased relative to placebo and showed similar patterns of response, with higher levels in the placebo group in serologically positive adult participants. In baseline seropositive individuals, GMTs at baseline were 7,541.0 and 3,062.2 EU/mL in the placebo and NVX-CoV2373 group, compared to 6,174.6 and 119,620.4 EU/mL at Day 35.

Neutralising antibody levels in serologically negative adult participants at Day 35 (Table 13) were increased relative to placebo across all age groups: ≥18 years of age, 18 to <65 years, and ≥65 years of age.

Table 7. Summary on neutralising antibodies for SARS-COV-2 wild-type virus at day 0 (baseline) and day 35 (14 days after second vaccination) in serologically negative participants by age groups (PP-IMM analysis set).

Parameter	Participants ≥ 18 Years		Participants 18 to < 65 Years		Participants ≥ 65 Years	
	NVX-CoV2373 N = 711	Placebo N = 333	NVX-CoV2373 N = 353	Placebo N = 163	NVX-CoV2373 N = 358	Placebo N = 170
Day 0 (baseline)[1]						
n1	708	331	351	161	357	170
Median (1/dilution)	10.0	10.0	10.0	10.0	10.0	10.0
Min, max (1/dilution)	10, 10240	10, 20	10, 10240	10, 10	10, 2560	10, 20
GMT	10.5	10.1	10.6	10.0	10.4	10.1
95% CI[2]	10.2, 10.9	10.0, 10.1	10.1, 11.2	10.0, 10.0	10.0, 10.9	10.0, 10.3
Day 35						
n1	703	332	349	163	354	169
Median (1/dilution)	1280.0	10.0	1280.0	10.0	1280.0	10.0
Min, max (1/dilution)	10, 40960	10, 640	10, 40960	10, 640	10, 20480	10, 640
GMT	1078.2	10.7	1292.8	10.6	901.6	10.8
95% CI[2]	968.0, 1200.9	10.2, 11.2	1128.0, 1481.6	9.9, 11.4	764.4, 1063.4	10.1, 11.6
n2	700	330	347	161	353	169
GMFR referencing Day 0	102.8	1.1	122.7	1.1	86.4	1.1
95% CI[2]	91.9, 115.1	1.0, 1.1	106.0, 142.2	1.0, 1.1	73.0, 102.4	1.0, 1.1
SCR ≥ 4-fold increase, n3/n2 (%)[3]	674/700 (96.3)	7/330 (2.1)	341/347 (98.3)	3/161 (1.9)	333/353 (94.3)	4/169 (2.4)
95% CI[4]	94.6, 97.6	0.9, 4.3	96.3, 99.4	0.4, 5.3	91.4, 96.5	0.6, 5.9

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

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

Note, titer values less than LLOQ (20) were replaced by 0.5 × LLOQ.
Source: T14.2.8.1.1

At 2 weeks following second vaccination in most participants (Day 35), neutralising antibody GMTs in the NVX-CoV2373 group were markedly increased relative to placebo for all participants (1,156.6 vs 11.8, respectively); for serologically positive participants (3,741.9 vs 190.3) relative to placebo; and for serologically negative participants (1,078.2 vs 10.7), with no evidence of placebo response (Table 14). Neutralising antibody GMTs in the NVXCoV2373 group were approximately 3.5-fold higher in the serologically positive cohort than in the serologically negative cohort. SCRs in the NVX-CoV2373 group also were markedly increased relative to placebo across all baseline serostatus groups (95.5% vs 2.3% for serologically negative and positive participants; 96.3% vs 2.1% for serologically negative participants; and 82.9% vs 8.3% for serologically positive participants).

Table 8. Summary of neutralising antibodies for SARS-COV-2 wild type virus at day 0 (baseline) and day 35 (14 days after second vaccination) in adult participants by baseline status (PP-IMM-2 Analysis set)

Parameter	Seropositive or Positive		Seronegative		Seropositive	
	NVX-CoV2373 N = 753	Placebo N = 345	NVX-CoV2373 N = 711	Placebo N = 333	NVX-CoV2373 N = 42	Placebo N = 12
Day 0 (baseline)[1]						
n1	749	343	708	331	41	12
Median (1/dilution)	10.0	10.0	10.0	10.0	160.0	160.0
Min, max (1/dilution)	10, 10240	10, 5120	10, 10240	10, 20	10, 5120	20, 5120
GMT	12.2	11.1	10.5	10.1	160.0	179.6
95% CI[2]	11.5, 13.0	10.4, 11.9	10.2, 10.9	10.0, 10.1	97.4, 262.9	52.5, 613.8
Day 35						
n1	745	344	703	332	42	12
Median (1/dilution)	1280.0	10.0	1280.0	10.0	2560.0	160.0
Min, max (1/dilution)	10, 40960	10, 1280	10, 40960	10, 640	320, 40960	20, 1280
GMT	1156.6	11.8	1078.2	10.7	3741.9	190.3
95% CI[2]	1041.2, 1284.7	11.0, 12.8	968.0, 1200.9	10.2, 11.2	2754.9, 5082.5	81.9, 441.8
n2	741	342	700	330	41	12
GMFR referencing Day 0	94.6	1.1	102.8	1.1	22.8	1.1
95% CI[2]	84.5, 105.9	1.0, 1.1	91.9, 115.1	1.0, 1.1	13.4, 38.9	0.6, 1.9
SCR ≥ 4-fold increase, n3/n2 (%)[3]	708/741 (95.5)	8/342 (2.3)	674/700 (96.3)	7/330 (2.1)	34/41 (82.9)	1/12 (8.3)
95% CI[4]	93.8, 96.9	1.0, 4.6	94.6, 97.6	0.9, 4.3	67.9, 92.8	0.2, 38.5

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

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

Note, titer values less than LLOQ (20) were replaced by 0.5 × LLOQ.
Source: T14.2.8.1.2

2019nCoV-302

Study 2019nCoV-302 is an ongoing Phase 3, multicentre, randomised, observer-blinded, placebo-controlled study in participants 18 to 84 years of age in the United Kingdom. Upon enrolment, participants were stratified by age (18 to 64 years; 65 to 84 years) to receive Nuvaxovid or placebo.

The main immunogenicity related endpoints were the analysis of antibodies binding to the SARS-CoV-2 S protein by ELISA, and SARS-CoV-2 neutralisation, both at Day 0 (baseline) and Day 35 (14 days after second study vaccination).

At 2 weeks following second vaccination in all participants (Day 35), serum anti-S IgG GMTs in the NVX-CoV2373 group were markedly increased approximately 350- to 400-fold relative to placebo across all age groups (44,673.8 vs 113.2 EU/mL, respectively, for participants 18 to 84 years of age; 47,564.3 vs 113.5 EU/mL for participants 18 to 64 years of age; and 37,892.8 vs 112.3 EU/mL for participants 65 to 84 years of age) with no evidence of placebo response. Serum anti-S IgG GMTs in the NVX-CoV2373 group were approximately 1.3-fold higher in the younger age cohort (18 to 64 years) than in the older age cohort (65 to 84 years). SCRs in the NVX-CoV2373 groups also were markedly increased relative to placebo across all age groups (99.0% vs 0.7% for participants 18 to 84 years of age; 99.0% vs 1.0% for participants 18 to 64 years of age; and 99.1% vs 0% for participants 65 to 84 years of age).

Serum anti-S IgG levels at Day 35 in both serologically negative and serologically positive adult participants were increased relative to placebo and showed similar patterns of response, with higher levels in the placebo group in serologically positive adult participants. In baseline seropositive individuals, GMTs at baseline were 1771.7 and 1698.8 EU/mL in the placebo and NVX-CoV2373 group, compared to 1756.9 and 125489.8 EU/mL at Day 35.

Neutralising antibody levels in serologically negative adult participants at Day 35 were increased relative to placebo across all age groups: 18 to 84 years, 18 to 64 years, and 65 to 84 years (Table 15).

Table 9. Summary of Neutralising Antibodies at Day 0 (Baseline) and Day 35 (14 Days after Second Vaccination) in Serologically Negative Adult Participants by Age Group (PP-IMM Neutralisation Assay Subset, 2019nCoV-302)

Parameter	Participants 18 to 84 Years		Participants 18 to 64 Years		Participants 65 to 84 Years	
	NVX-CoV2373 N = 381	Placebo N = 380	NVX-CoV2373 N = 270	Placebo N = 284	NVX-CoV2373 N = 111	Placebo N = 96
Day 0 (baseline)[1]						
n1	381	380	270	284	111	96
Median	10.0	10.0	10.0	10.0	10.0	10.0
Min, max	10, 160	10, 40	10, 20	10, 40	10, 160	10, 10
GMT	10.1	10.1	10.1	10.1	10.3	10.0
95% CI[2]	10.0, 10.3	10.0, 10.2	10.0, 10.1	10.0, 10.2	9.8, 10.8	10.0, 10.0
Day 35 (14 days after second vaccination)						
n1	381	380	270	284	111	96
Median	1280.0	10.0	1280.0	10.0	1280.0	10.0
Min, max	10, 20480	10, 5120	10, 20480	10, 5120	10, 10240	10, 10
GMT	1133.1	10.4	1241.2	10.5	907.9	10.0
95% CI[2]	999.4, 1284.7	9.9, 10.8	1069.4, 1440.5	9.9, 11.1	720.1, 1144.8	10.0, 10.0
GMFR referencing Day 0	112.1	1.0	123.5	1.0	88.6	1.0
95% CI[2]	98.7, 127.3	1.0, 1.1	106.4, 143.3	1.0, 1.1	69.4, 113.0	1.0, 1.0
SCR ≥ 4-fold increase[3], n2/n1 (%)	374/381 (98.2)	2/380 (0.5)	265/270 (98.1)	2/284 (0.7)	109/111 (98.2)	0/96 (0.0)
95% CI[4]	96.3, 99.3	0.1, 1.9	95.7, 99.4	0.1, 2.5	93.6, 99.8	0.0, 3.8

Abbreviations: CI = confidence interval; GMFR = geometric mean fold rise; GMT = geometric mean titer; LLOQ = lower limit of quantification; max = maximum; Min = minimum; n1 = number of participants in the PP-IMM Neutralization Assay Subset; n2 = number of participants who reported ≥ 4-fold increase, with percentages calculated as (n2/n1) × 100; NVX-CoV2373 = 5 µg SARS-CoV-2 rS with 50 µg Matrix-M1 adjuvant; PP-IMM = Per-Protocol Immunogenicity; SARS-CoV-2 rS = severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine; SCR = seroconversion rate.

1. Baseline was defined as the last non-missing assessment prior to first vaccination.
2. The 95% CI for GMT and GMFR were calculated based on the t-distribution of the log-transformed values then back transformed to the original scale for presentation.
3. The SCR was defined as percentage of participants at each post vaccination visit with a titer ≥ 4-fold rise.
4. The 95% CI for SCR was calculated using the exact Clopper-Pearson method.

Note: LLOQ = titer of 20, with titer values less than LLOQ were replaced by 0.5 × LLOQ.
Source: T14.2.8.2.1

At 2 weeks following second vaccination (Day 35), neutralising antibody GMTs in the NVX-CoV2373 group were markedly increased approximately 110-fold relative to placebo for serologically negative participants (1,129.5 vs 10.4); and approximately 70-fold for serologically positive participants (4,373.8 vs 62.0) with no evidence of placebo response (Table 16). Neutralising antibody GMTs in the NVXCoV2373 group were approximately 3.9-fold higher in the serologically positive cohort than in the serologically negative cohort. SCRs in the NVX-CoV2373 group also were markedly increased relative to placebo across baseline serostatus groups (98.2% vs 0.8% for serologically negative participants; and 100.0% vs 15.8% for serologically positive participants).

Table 10 Summary of Neutralising Antibody Levels at Day 0 (Baseline) and Day 35 (14 Days after Second Vaccination) in Adult Participants By Baseline Serostatus (ITT Neutralisation Assay Subset, 2019nCoV-302)

Parameter	Seropositive or Positive		Seronegative		Seropositive	
	NVX-CoV2373 N = 500	Placebo N = 497	NVX-CoV2373 N = 473	Placebo N = 475	NVX-CoV2373 N = 24	Placebo N = 20
Day 0 (baseline)[1]						
n1	410	409	388	390	22	19
Median	10.0	10.0	10.0	10.0	60.0	40.0
Min, max	10, 1280	10, 1280	10, 160	10, 40	10, 1280	10, 1280
GMT	11.1	10.8	10.1	10.1	58.4	48.0
95% CI[2]	10.6, 11.7	10.4, 11.3	10.0, 10.3	10.0, 10.2	33.7, 101.3	28.2, 81.7
Day 35 (14 days after second vaccination)						
n1	410	409	388	390	22	19
Median	1280.0	10.0	1280.0	10.0	5120.0	80.0
Min, max	10, 20480	10, 5120	10, 20480	10, 5120	640, 10240	10, 2560
GMT	1214.6	11.3	1129.5	10.4	4373.8	62.0
95% CI[2]	1074.1, 1373.6	10.6, 12.1	996.9, 1279.8	10.0, 10.9	3109.8, 6151.4	31.4, 122.2
GMFR referencing Day 0	109.4	1.0	111.7	1.0	74.9	1.3
95% CI[2]	96.8, 123.6	1.0, 1.1	98.5, 126.8	1.0, 1.1	48.1, 116.8	0.8, 2.0
SCR ≥ 4-fold increase[3], n2/n1 (%)	403/410 (98.3)	6/409 (1.5)	381/388 (98.2)	3/390 (0.8)	22/22 (100.0)	3/19 (15.8)
95% CI[4]	96.5, 99.3	0.5, 3.2	96.3, 99.3	0.2, 2.2	84.6, 100.0	3.4, 39.6

Abbreviations: CI = confidence interval; GMFR = geometric mean fold rise; GMT = geometric mean titer; ITT = Intent-to-Treat; LLOQ = lower limit of quantification; max = maximum; Min = minimum; n1 = number of participants in the ITT Neutralization Assay Subset; n2 = number of participants who reported ≥ 4-fold increase, with percentages calculated as (n2/n1) × 100; NVX-CoV2373 = 5 µg SARS-CoV-2 rS with 50 µg Matrix-M1 adjuvant; SARS-CoV-2 rS = severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine; SCR = seroconversion rate.

1. Baseline was defined as the last non-missing assessment prior to first vaccination.
2. The 95% CI for GMT and GMFR were calculated based on the t-distribution of the log-transformed values then back transformed to the original scale for presentation.
3. The SCR was defined as percentage of participants at each post vaccination visit with a titer ≥ 4-fold rise.
4. The 95% CI for SCR was calculated using the exact Clopper-Pearson method.

Note: LLOQ = titer of 20, with titer values less than LLOQ were replaced by 0.5 × LLOQ.
Source: T14.2.8.2.2

An authorised seasonal influenza co-administration substudy was conducted as part of protocol 2019nCoV-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).

The objective of the substudy was to evaluate the safety and immunogenicity of SARS-CoV-2 rS with Matrix-M1 adjuvant in the initial set of vaccinations when co-administered with an authorised seasonal influenza vaccine. The endpoint was *Analysis of the safety and immunogenicity of SARS-CoV-2 rS with Matrix-M1 adjuvant when co-administered with seasonal influenza vaccine in a subset population*.

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.

- Flucelvax contains surface antigens (hemagglutinin and neuraminidase) detergent-extracted from the 4 strains of influenza virus recommended annually by the WHO for the Northern Hemisphere season (type A H1N1, type A H3N2, type B Yamagata lineage and type B Victoria lineage; 15 ug virus protein of each, 60 ug virus protein in total).
- Fluad contains surface antigens (hemagglutinin and neuraminidase) detergent-extracted from type A H1N1, type A H3N2 and type B Victoria virus, adjuvanted with MF59 (oil-in-water emulsion of squalene, a metabolisable oil).
- Flucelvax is authorised in the EU but the trivalent Fluad is not; however, in the EU, a tetravalent version of Fluad is available.

The results are shown in the following two tables for the Hemagglutination Inhibition Assay and the Serum Anti-Spike Protein Binding IgG Specific to SARS-CoV-2 rS Protein Antigen Assay, respectively.

Table 11. Summary of Hemagglutination Inhibition Assay by Influenza Virus Strain at Day 0 and Day 21 in Adult Participants Who Were Co-Administered QIVc and aTIV at Day 0 by Age Group (PP-IMM HAI Serology Subset)

Influenza Virus Strain	Participants 18 to 84 Years (aTIV + QIVc)		Participants 18 to 64 Years (QIVc)		Participants 65 to 84 Years (aTIV)	
	NVX-CoV2373 N = 191	Placebo N = 190	NVX-CoV2373 N = 178	Placebo N = 179	NVX-CoV2373 N = 13	Placebo N = 11
Influenza A H1N1 (HAI titre)						
GMT day 0	**11.8**	**12.8**	**11.1**	**13.4**	**28.8**	**5.8**
95%CI day 0	9.6, 14.7	10.4, 15.7	8.9, 13.8	10.8, 16.6	10.5, 78.9	2.9, 11.8
GMT day 21	**195.7**	**158.7**	**198.0**	**162.1**	**167.1**	**112.8**
95%CI day 21	160.1, 239.3	130.1, 193.6	160.2, 244.6	132.3, 198.7	85.2, 327.9	39.2, 325.1
GMFR	16.5	12.4	17.8	12.1	5.8	19.3
Influenza A H3N2 (HAI titre)						
GMT day 0	**35.8**	**36.2**	**35.1**	**36.8**	**46.5**	**28.2**
95%CI day 0	28.9, 44.4	29.1, 45.2	28.2, 43.8	29.2, 46.3	14.8, 145.6	12.0, 66.3
GMT day 21	**246.9**	**219.6**	**253.0**	**221.0**	**176.3**	**199.0**
95%CI day 21	216.2, 281.9	189.2, 255.0	220.9, 289.9	189.3, 258.0	93.8, 331.3	102.1, 387.8
GMFR	6.9	6.1	7.2	6.0	3.8	7.1
Influenza B Virus Victoria (HAI titre)						
GMT day 0	**3.4**	**3.2**	**3.3**	**3.3**	**4.7**	**2.9**
95%CI day 0	3.0, 3.9	2.9, 3.6	2.9, 3.8	2.9, 3.7	2.4, 9.3	1.7, 5.1
GMT day 21	**9.9**	**9.7**	**9.8**	**9.2**	**11.0**	**21.9**
95%CI day 21	8.0, 12.2	8.0, 11.7	7.9, 12.2	7.6, 11.2	4.6, 26.2	8.6, 56.1
GMFR	2.9	3.0	3.0	2.8	2.3	7.5
Influenza B Virus Yamagata (HAI titre)						
GMT day 0	**8.1**	**8.8**	**8.0**	**8.8**	**9.9**	**7.5**
95%CI day 0	6.7, 9.8	7.3, 10.5	6.6, 9.7	7.3, 10.7	3.9, 25.0	4.1, 13.8
GMT day 21	**36.9**	**36.5**	**39.2**	**38.1**	**16.0**	**18.1**
95%CI day 21	30.4, 44.7	31.0, 43.0	32.2, 47.7	32.2, 45.0	7.0, 36.3	8.4, 39.4
GMFR	4.6	4.2	4.9	4.3	1.6	2.4

Table 12 Summary of Serum Anti-S IgG Levels at Day 0 (Baseline) and Day 35 (14 Days after Second Vaccination) in Serologically Negative Adult Participants Who Were Co-Administered QIVc and aTIV at Day 0 by Age Group (PP-IMM Anti-S Protein Serology Subset of the Seasonal Influenza Vaccine Substudy)

SARS-CoV-2	Participants 18 to 84 Years (aTIV + QIVc)		Participants 18 to 64 Years (QIVc)		Participants 65 to 84 Years (aTIV)	
	NVX-CoV2373 N = 178	Placebo N = 181	NVX-CoV2373 N = 168	Placebo N = 170	NVX-CoV2373 N = 10	Placebo N = 11
Anti-S IgG levels, measured by ELISA						
GMT day 0	**116.3**	**111.4**	**115.8**	**112.2**	**125.6**	**100.0**
95%CI day 0	107.7, 125.6	105.1, 118.1	107.2, 125.0	105.4, 119.3	75.0, 210.3	100.0, 100.0
GMT day 35	**31236.1**	**115.7**	**31516.9**	**116.8**	**26876.1**	**100.0**
95%CI day 35	26295.5, 37104.9	106.1, 126.1	26316.2, 37745.3	106.6, 128.0	15374.6, 46981.5	100.0, 100.0
GMFR	268.6	1.0	272.3	1.0	214.0	1.0
Anti-S IgG levels, measured by ELISA (full PP-IMM subset)						
	NVX-CoV2373 N = 414	*Placebo N = 417*	*NVX-CoV2373 N = 300*	*Placebo N = 310*	*NVX-CoV2373 N = 114*	*Placebo N = 107*
GMT day 0	*112.2*	*110.3*	*111.9*	*109.7*	*112.8*	*112.1*
95%CI day 0	*107.5, 117.0*	*106.3, 114.5*	*106.2, 117.9*	*105.2, 114.4*	*105.0, 121.2*	*103.4, 121.4*
GMT day 35	*44678.3*	*113.2*	*47564.3*	*113.5*	*37892.8*	*112.3*
95%CI day 35	*40352.2, 49468.2*	*106.8, 120.0*	*42327.3, 53449.4*	*105.6, 122.0*	*30833.3, 46568.5*	*103.1, 122.3*
GMFR	*398.4*	*1.0*	*425.0*	*1.0*	*335.9*	*1.0*

Co-administration resulted in no change to influenza vaccine immune responses as measured by hemagglutination inhibition (HAI) assay. A 30% reduction in antibody responses to Nuvaxovid was noted as assessed by an anti-spike IgG assay with seroconversion rates similar to participants who did not receive concomitant influenza vaccine. The clinical impact of the reduced response is unknown.

2019nCoV-501

2019nCoV-501 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 18 to 64 years of age in South Africa. These people 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. Upon enrolment, participants were randomly assigned to receive Nuvaxovid or placebo.

Immunogenicity related endpoints considered binding antibody levels and neutralising antibody activity at Day 0, 21 (only for binding antibodies) and 35 in healthy HIV-negative and medically stable HIV-positive adult subjects with baseline negative serostatus, baseline positive serostatus, or regardless of baseline serostatus.

Regardless of HIV status, anti-S IgG antibody GMTs at Day 0 were higher for participants who were seropositive at baseline, across both vaccine and placebo groups, than they were for participants who were seronegative at baseline.

In all participants (HIV seronegative and HIV seropositive subjects together), SARS-CoV-2 seronegative at baseline, the anti-S IgG antibody GMT at Day 21 was greater for participants who received NVX-CoV2373 (1,147.4 EU/mL) than it was for those who received placebo (119.2 EU/mL). The anti-S IgG antibody GMT further increased after the second dose, to 30520.6 and 126.0 EU/mL at Day 35.

Among participants who were SARS-CoV-2 seronegative at baseline, anti-S IgG antibody GMTs for HIV-positive participants were approximately half of those seen for HIV-negative participants (14420.5 vs 31631.8 EU/mL at Day 35); however, among participants who were SARS-CoV-2 seropositive at baseline, anti-S IgG antibody GMTs for HIV-positive participants were comparable to those seen for HIV-negative participants (98399.5 vs 100666.1 EU/mL at Day 35).

In all participants, regardless of baseline serostatus and regardless of HIV status, participants who received 2 doses of NVX-CoV2373 showed stronger neutralising antibody responses, in terms of amplitude and kinetics, than did those that received placebo. Also in this study, among participants who were SARS-CoV-2 seropositive at baseline, neutralising antibody GMTs for HIV-positive participants were comparable to those seen for HIV-negative participants. Regardless of HIV status, SARS-CoV-2 wild-type virus neutralising antibody GMTs at Day 35 were markedly higher in seropositive as compared to seronegative participants. SCRs at Day 35 ranged from 92.3% to 98.4% for NVX-CoV2373 versus 2.0% to 13.5% for placebo for all actively immunised participants and for HIV-negative and HIV-positive participants with baseline negative serostatus, baseline positive serostatus, or regardless of baseline serostatus. See Table 19 below for more details per HIV serostatus group.

Table 13 Summary of Serum Neutralising Antibody Levels Specific for SARS-CoV-2 Wild-Type Virus at Day 35 Following Vaccination with SARS-CoV-2 rS and Matrix-M1 Adjuvant in All Participants (HIV negative and HIV positive) Stratified by Baseline Serostatus – Comparison of Vaccine and Placebo Groups (PP Immunogenicity Analysis Set)

	HIV negative participants				HIV positive participants			
	Baseline seronegative		Baseline seropositive		Baseline seronegative		Baseline seropositive	
	NVX-CoV2373	Placebo	NVX-CoV2373	Placebo	NVX-CoV2373	Placebo	NVX-CoV2373	placebo
Baseline								
n	1255	1187	680	734	63	65	39	38
GMT	**10.2**	**10.3**	**56.9**	**52.3**	**10.4**	**10.4**	**74.5**	**70.4**
95% CI	10.1, 10.3	10.1, 10.4	51.7, 62.7	47.6, 57.3	10.0, 10.9	9.9, 11.0	48.3, 115.0	48.3, 102.7
Day 35								
n	1224	1161	650	700	61	64	39	37
GMT	**714.7**	**10.8**	**3105.0**	**64.4**	**320.0**	**12.0**	**2748.6**	**61.5**
95% CI	664.7, 768.5	10.5, 11.1	2823.3, 3414.9	58.3, 71.2	228.1, 448.9	10.6, 13.6	1478.2, 5110.9	39.5, 95.9
GMFR vs. Day 0	70.4	1.1	53.4	1.2	30.6	1.2	36.9	0.9
SCR ≥ 4-fold increase, n2/n1 (%)	1188/1224 (97.1)	23/1161 (2.0)	633/650 (97.4)	94/700 (13.4)	60/61 (98.4)	4/64 (6.3)	36/39 (92.3)	5/37 (13.5)

2.6.3. Discussion on clinical pharmacology

In the context of vaccines, PK studies are not required because the PK is not considered informative towards the determination of an optimal dose and the metabolic pathways of vaccines are generally understood.

The applicant has performed several assays to characterise the vaccine-induced immune response. At the present time, there is no established immunological correlate of protection against SARS-CoV-2 infection. Current evidence suggests that neutralising antibody against the spike protein of SARS-CoV-2 is likely to be the best surrogate marker for vaccine efficacy.

Validation reports have been submitted for the main assays, including the SARS-CoV-2 microneutralisation (MN) assay and the IgG ELISA. The T cell assays have not yet been validated. If these assays will be used for the analysis of phase 3 study samples, validation reports are expected to be available. Of note, the validation exercise should include all steps, i.e. also the preparation, freezing and shipping of vaccinee PBMCs, and bridging studies between US and UK laboratories.

For both the MN and IgG ELISA assays efforts have been put in calibrating the assay standards with the WHO international standard (IS). For the S-binding ELISA, the conversion factor to convert IgG antibody level from EU/mL to BAU/mL is calculated to be 22. As such, any antibody level depicted in ELISA units can be divided by 22 to express these in the WHO international units BAU/mL. For the MN assay, a conversion factor of 0.62 has been determined.

Immunogenicity data available were generated from study 2019nCoV-101 part 1 and 2 (dose response studies), 2019nCoV-302, 2019nCoV-301 (main studies), and 2019nCoV-501 (supportive study). Immunogenicity was assessed primarily based on circulating neutralising and spike antigen-binding antibodies as measured by in vitro SARS-CoV-2 neutralisation assay and anti-S protein IgG binding ELISA, respectively. Results from an hACE2 receptor binding inhibition ELISA and a limited amount of T cell immunity data were also included in the interim report of study 2019nCoV-101. The clinical phase 1/2 immunogenicity findings were in concordance with the preclinical immunogenicity findings in mice,

hamsters and nonhuman primate models; both preclinical and clinical data supports the posology intended for authorisation (5 ug of SARS-CoV-2 rS spike protein antigen adjuvanted with 50 ug of Matrix-M1). T cell responses were Th1-skewed.

Clinical phase 3 data confirm that the vaccine is immunogenic and the studied two dose schedule resulted in seroconversion in almost all participants. Also, in baseline seropositive subjects, the 2-dose regimen resulted in a markedly increased humoral immune response. Whether or not a single dose would also suffice in this subgroup is unknown, as data after a single dose have not been collected in the pivotal study.

As expected, immune responses were somewhat lower in the adults ≥ 65 years of age, as well as in HIV seropositive participants (for the latter group in both subgroups antibodies (binding and neutralising) were approximately 2-fold reduced). These findings raise no immediate concerns, but the magnitude as well as durability of immunogenicity of the vaccine in elderly subjects as well as medically stable HIV-positive subjects remains to be determined based on final study data. It is agreed that based on the available data, no dose adjustment is required in adults ≥ 65 years of age as also stated in the SmPC.

In healthy COVID-19 naïve individuals 18-64 years of age of study 2019nCOV-101, at day 189 (approximately 5 months after the second dose), binding as well as functional antibody levels were approximately 10-fold reduced compared to the maximum at day 35; seroconversion rates remained at 100% for binding antibodies, but had declined to ≥ 64% for neutralising antibodies. The clinical relevance hereof, and whether or not (and if so, when) a booster dose should be recommended is currently unknown.

Across all studies, few non-responders were seen for both the binding antibody as well as neutralisation assay. Lower immune response was observed in study 2019nCoV-501 (conducted in South-Africa) as compared to study 2019nCoV-302 (conducted in the UK). Furthermore, a lower vaccine efficacy has been reported for study 2019nCoV-501 as compared to 2019nCoV-302 (see clinical efficacy section for more details). Although there are differences between the assays used in the two studies that may explain some of the observed differences in response levels, a resolutive explanation for the lower levels of neutralising antibody responses reported from Clinical Study 2019nCoV-501 has not been found. Importantly, the applicant states that no issues have been observed with the shipping or storage of the study vaccine in study 2019nCoV-501 (such as temperature excursions) that might have contributed to the reduced response levels. The reduced efficacy seen in study 2019nCoV-501 is according to the applicant directly attributable to the emergence of the Beta escape variant in South Africa during the study. While it is acknowledged that the emergence of the Beta variant likely has had a role in the reduced efficacy, it cannot be excluded that there are other factors that may have affected overall vaccine efficacy. However, given the lack of solid explanations as to why the immunogenicity was lower in 2019nCoV-501 and whether this can be linked to the reduced efficacy, no further action is currently required. The applicant is currently performing an analysis of immune correlates of risk and protection from the pre-crossover efficacy period for Clinical Study 2019nCoV-301 which may be able to provide additional insight in the implications of the observed lower immunogenicity in study 2019nCoV-501.

A diminished response was also observed in participants in study 2019nCoV-302 who received a concomitant seasonal influenza vaccination (approx. 1.5-fold). The clinical impact of the reduced response is unknown. The few cases of PCR-confirmed symptomatic mild, moderate, or severe COVID-19 observed in the substudy population (n=10 in total, 2 in the active arm and 8 in the placebo arm) are considered insufficient to dismiss the concern. SARS-CoV-2 neutralising antibody responses for the influenza substudy participants were not investigated by the applicant. Also, while negative impact of non-adjuvanted (quadrivalent) flu vaccine on NVX-CoV2373 is not expected, interactions between

NVX-CoV2373 (adjuvanted with Matrix-M1) and adjuvanted flu vaccines (e.g. MF59-adjuvanted trivalent flu vaccine such as used in study 2019nCoV-302) cannot be ruled out, especially if accidentally injected at the same site, because of the similarity in the modes of action between the adjuvants present in the vaccines. However, in study 2019nCoV-302, only elderly participants received adjuvanted trivalent flu vaccine, and there are too few elderly participants in the influenza sub-study for conclusions to be drawn. In short, the data from the flu substudy is considered too limited to support any recommendations regarding concomitant use of NVX-CoV2373 with influenza vaccines.

Different PCR assays have been used in the different studies. All assays were however validated and expected to perform well.

Further, sequencing of breakthrough cases has been performed. More information, including on the CT values of all positive samples, by virus strain (Wuhan vs. B.1.1.7, vs. other variants) will be provided in later CSRs.

Several issues remain that require further investigation and that may be solved post-authorisation. These include i) investigation on the need of a booster dose; ii) investigation on identifying an immunological correlate of protection, and iii) investigation (with regular updates) on the ability of the vaccine to neutralise emerging SARS-CoV-2 variants.

2.6.4. Conclusions on clinical pharmacology

In conclusion, aspects related to clinical pharmacology have been satisfactory addressed by the applicant. The immune response data provided in the interim reports overall support the choice of a 2-dose schedule of NVX-CoV2373, with no apparent advantage for 25 vs. 5 µg antigen doses in the adjuvanted formulations.

The interim immunogenicity data indicates that immunogenicity is likely reduced in the elderly and HIV-positive subjects; the magnitude of this reduction remains to be determined. No conclusions can currently be reached on (i) durability of immune responses (especially in elderly vaccinees), and concomitant use of NVX-CoV2373 with influenza vaccines (especially adjuvanted influenza vaccines).

The CHMP considers the following measures necessary to address the issues related to pharmacology: the applicant should submit final study reports from studies 2019nCoV-101 part 1 and 2, 2019nCoV-301, 2019nCoV-302 and 2019nCoV-501 as soon as these are available, investigate the need of a booster dose, detail their plans to establish an immunologic correlate of protection, and investigate (with regular updates) the ability of the vaccine to neutralise emerging SARS-CoV-2 variants**.**

2.6.5. Clinical efficacy

2.6.5.1. Dose response studies

See section 2.6 on clinical pharmacology for an overview of the immunogenicity data from dose finding study 2019nCoV-101, Part 1 and Part 2.

Overall, the safety and immunogenicity data obtained in Part 1 and Part 2 of 2019nCoV-101 provided support for the inclusion of the adjuvant and administration of a second dose, with no apparent advantage for 25 vs. 5 µg antigen doses in the adjuvanted formulations. The immunogenicity analyses by age subgroup (humoral immunity only) show a potent response in both age groups, although the magnitude of the response was consistently lower in the older age stratum. The clinical relevance of this lower response can however not yet be determined. Clinical efficacy information for this age

stratum will come from the main studies described below. Reactogenicity was higher in the adjuvanted arms of the study and 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).

2.6.5.2. Main studies

Two pivotal studies are included for this MAA: 2019nCoV-301 and 2019nCoV-302. These are phase 3, randomised, observer-blinded, placebo-controlled trials designed to evaluate the efficacy and safety of a SARS-CoV-2 rS with Matrix-M1 adjuvant in adult participants 18 years of age and older in the US, Mexico for study 2019nCoV-301 and the United Kingdom 2019nCoV-302.

Study 2019nCoV-301 & 2019nCoV-302

Methods

Study 2019nCoV-301 & Study 2019nCoV-302 were presented together for the similar study sections, while they were reported separately to explain differences as needed.

Study Participants

The trials included healthy male or female participants aged 18 to 84 years (2019nCoV-302) or 18 years and older (2019nCoV-301), 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. Both trials 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.

Treatments

Participants were randomised to either 2 doses of 5 µg SARS-CoV-2 rS with 50 µg Matrix-M1 adjuvant (NVX-CoV2373) or saline placebo (Sodium chloride injection (BP, sterile), 0.9%).

In 2019nCoV-302, single dose vials manufactured from Emergent BioSolutions (Emergent) were used. Lot numbers were 2870-101 and 2870-102. The seasonal influenza vaccine co-administration sub-study will comprise a single IM injection (0.5 mL) of an authorised influenza vaccine on Day 0 in an open-label manner. An unadjuvanted quadrivalent influenza vaccine will be given to those 18 to 64 years of age, and an adjuvanted trivalent influenza vaccine will be given to those ≥ 65 years of age.

In study 2019nCoV-301, material filled in multi-dose vials (MDV), manufactured by Par Pharmaceutical was used. The lot number was from Drug Product Lot 280003 manufactured at Par Pharmaceuticals, Inc. The lot was composed of drug substance and Matrix-M1, Lot GR1350007, manufactured at FujiFilm Diosynth Biotechnologies (FDBU) at the 2000 L scale. For information with regards to comparability between the batches produced at the two sites please see the sections 2.4 on Quality aspects. Of note, there are differences between the batches used in the different trials. In study 2019nCoV-301 the DP Lot PAR28003 was used which had a higher level of protein as well as higher levels of impurities compared to the DP Lots EBSI DP4 and EBSI DP5 used in trial 2019nCoV-302, as well as in trial 2019nCoV-101 and 2019nCoV-501. The commercial batches are more comparable to the lots used in the 2019nCOV-301 trial.

Objectives

2019nCoV-301

Primary Efficacy objective:

- To evaluate the efficacy of a 2-dose regimen of SARS-CoV-2 rS adjuvanted with Matrix-M1 compared to placebo against PCR-confirmed symptomatic coronavirus disease 2019 (COVID-19) illness diagnosed ≥ 7 days after completion of the second injection in the initial set of vaccinations of adult participants ≥ 18 years of age.

Secondary Efficacy objectives:

- To evaluate the efficacy of a 2-dose regimen of SARS-CoV-2 rS adjuvanted with Matrix M1 compared to placebo against PCR-confirmed symptomatic COVID-19 illness due to a SARS-CoV-2 variant not considered as a "variant of concern / interest" according to the CDC Variants Classification diagnosed ≥ 7 days after completion of the second injection in the initial set of vaccinations of adult participants ≥ 18 years of age.
- To evaluate the efficacy of a 2-dose regimen of SARS-CoV-2 rS adjuvanted with Matrix-M1 compared to placebo against PCR-confirmed moderate-to-severely symptomatic COVID-19 illness diagnosed ≥ 7 days after completion of the second injection in the initial set of vaccinations of adult participants ≥ 18 years of age.
- To assess vaccine efficacy (VE) against ANY symptomatic SARS-CoV-2 infection.
- To assess VE according to race and ethnicity.
- To assess VE in high-risk adults versus non-high-risk adults (high-risk is defined by age ≥ 65 years with or without co-morbidities or age < 65 years with co-morbidities [e.g., obesity (body mass index [BMI] ≥ 30 kg/m2), chronic kidney or lung disease, cardiovascular disease and diabetes mellitus type 2] and/or by life circumstance [living or working conditions involving known frequent exposure to SARS-CoV-2 or to densely populated circumstances (e.g., factory or meat packing plants, essential retail workers, etc)]).

Exploratory efficacy objectives:

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

2019nCoV-302

Primary Efficacy objective:

- To demonstrate the efficacy of SARS-CoV-2 rS with Matrix-M1 adjuvant in the prevention of virologically confirmed (by PCR to SARS-CoV-2), symptomatic COVID-19, when given as a 2-dose vaccination regimen, as compared to placebo, in serologically negative (to SARS-CoV-2) adults.

Secondary Efficacy objectives:

- To demonstrate the efficacy of SARS-CoV-2 rS with Matrix-M1 adjuvant in the prevention of virologically confirmed (by PCR to SARS-CoV-2), symptomatic COVID-19, when given as a 2-dose vaccination regimen, as compared to placebo, in adults regardless of their serostatus at baseline.
- To assess the efficacy of SARS-CoV-2 rS with Matrix-M1 adjuvant in adult participants requiring specific medical interventions as compared to placebo.

Exploratory Efficacy objectives:

- In a subset of adult participants, to evaluate the safety and immunogenicity of SARS CoV-2 rS with Matrix-M1 adjuvant when co-administered with an authorised seasonal influenza vaccine.

Outcomes/endpoints

Primary endpoint (2019nCoV-301, 2019nCoV-302):

For both pivotal studies the primary endpoint is defined as: the first episode of PCR-positive mild, moderate, or severe COVID-19 with onset at least 7 days after second study vaccination (e.g., Day 28), in serologically negative (to SARS-CoV-2) adult participants at baseline until the endpoint-driven efficacy analysis is triggered by the occurrence of a prespecified number of blinded endpoints. The definition of severity of the endpoint can be found in table 20 below.

Table 14. Endpoint Definitions of COVID-19 Severity (2019nCoV-301, 2019nCoV-302)

COVID-19 Severity	Endpoint Definitions
Mild	≥ 1 of: • Fever (defined by subjective or objective measure, regardless of use of anti-pyretic medications) • New onset cough • ≥ 2 COVID-19 respiratory/non-respiratory symptoms in Table 21 **AND** • Does not meet criteria for moderate or severe disease
Moderate	≥ 1 of: • Fever (defined by subjective or objective measure, regardless of use of anti-pyretic medications) + any 2 COVID-19 symptoms (Table 21) for ≥ 3 days (need not be contiguous days)[#] • High fever (≥ 38.4°C) for ≥ 3 days (need not be contiguous days[$]) • Any evidence of significant LRTI: – Shortness of breath (or breathlessness or difficulty breathing) with or without exertion (greater than baseline) – Tachypnoea: 20 to 29 breaths per minute at rest*[$] – SpO2: 94% to 95% on room air* – Abnormal chest x-ray or chest CT consistent with pneumonia or LRTI – Adventitious sounds on lung auscultation (e.g., crackles/rales, wheeze, rhonchi, pleural rub, stridor)

COVID-19 Severity	Endpoint Definitions
	AND • Does not meet criteria for severe disease
Severe	≥ 1 of: • Tachypnoea: ≥ 30 breaths per minute at rest* • Resting heart rate ≥ 125 beats per minute* • SpO_2: ≤ 93% on room air or PAO_2/FiO_2 < 300 mmHg* • High flow oxygen therapy or NIV/NIPPV (e.g., CPAP or BiPAP) • Mechanical ventilation or ECMO • One or more major organ system dysfunction or failure (e.g., cardiac/circulatory, pulmonary, renal, hepatic, and/or neurological, to be defined by diagnostic testing/clinical syndrome/interventions), including any of the following: o ARDS[$] o Acute renal failure o Acute hepatic failure o Acute right or left heart failure o Septic or cardiogenic shock (with shock defined as SBP < 90 mm Hg OR DBP < 60 mm Hg o Acute stroke (ischemic or haemorrhagic) o Acute thrombotic event: AMI, DVT, PE o Requirement for: vasopressors, systemic corticosteroids, or haemodialysis. • Admission to an ICU • Death

Abbreviations: AMI = acute myocardial infarction; ARDS = acute respiratory distress syndrome; BiPAP = bi-level positive airway pressure; CPAP = continuous positive air pressure; CT = computed tomography; DBP = diastolic blood pressure; DVT = deep vein thrombosis; ECMO = extracorporeal membrane oxygenation; FiO_2 = fraction of inspired oxygen; ICU = intensive care unit; LRTI = lower respiratory tract infection; NIV = non-invasive ventilation; NIPPV = non-invasive positive pressure ventilation; PAO_2 = partial pressure of oxygen in the alveolus; PE = pulmonary embolism; SBP = systolic blood pressure; SpO_2 = oxygen saturation.

[#] Only for study 2019nCoV-302

[$] In study 2019nCoV-301 fever measurements were regardless of the use of anti-pyretic medications; tachypnoea was defined as 24 to 29 breaths per minute at rest for moderate COVID. For severe COVID

*Participants with a single vital sign abnormality placing them in the moderate or severe categories must also meet the criteria for mild COVID-19.

Table 21 provides an overview of symptoms that would qualify for virological testing.

Table 21. Qualifying Symptoms of Suspected COVID-19

• Fever • New onset cough • New onset or worsening of shortness of breath or difficulty breathing compared to baseline • New onset fatigue • New onset generalised muscle or body aches • New onset headache • New loss of taste or smell • Acute onset of sore throat, congestion, and runny nose • New onset nausea, vomiting, or diarrhoea

Abbreviations: COVID-19 = coronavirus disease 2019.

In study **2019nCoV-301**, the eDiary would alert participants to start daily nasal self-swabbing for PCR testing within 3 days of symptom onset at home (3 days) and to initiate daily completion of the InFLUenza Patient-Reported Outcome (FLU-PRO) symptom reporting instrument for 10 days. Also, the eDiary alerted the study site to schedule a surveillance visit *(Unscheduled Acute Illness Visit),* which included taking of vital signs, a nasal swab and blood sample for serologic testing. PCR-positive swabs obtained outside the study from either asymptomatic participants, e.g. for travel or work, or from symptomatic infection not evaluated by swab(s) tested by the central laboratory, were not included in

the endpoint analyses. Active surveillance for COVID-19 will continue after the blinded crossover through the first 12 months of study. Passive surveillance of safety and efficacy via remote contacts or the scheduled visits will continue during months 12 to 24.

For information on the PCR assays used, see section 2.6.2 of Clinical Pharmacology.

In study **2019nCoV-302**, participants received weekly reminders (email or text messages) to immediately contact the study team if they have experienced any new symptoms or health concerns that could be related to infection with SARS-CoV-2. If a participant experiences any symptom included in Table 21, this will trigger:

- Nose/throat self-sampling once daily for 3 consecutive days. If any test is found to be positive before 3 consecutive days of testing is performed, the full 3 consecutive tests may not be required. Participants will self-sample based on the training given on Day 0.
- Nose/throat sampling will be started approximately 24 hours after the first symptom(s) are reported.
- Participants will take their temperature daily for 10 days and complete a FLU_PRO diary to record symptoms.

Study participants were discouraged from using non-study swabs; however, it was not prohibited. Non-study swabs include swabs taken during hospitalisations, ER visits, local tests performed at the study sites, or private testing facilities. If a valid report existed for testing in any of these conditions, it was treated identically to a study swab.

Newly discovered symptoms of suspected COVID-19 will trigger a COVID-19 Surveillance Visit. During the surveillance visit, symptoms will be reviewed and confirmed, vital signs will be taken, any health care visits will be documented and use of concomitant medication recorded.

Secondary endpoints 2019nCoV-301:

- First episode of PCR-positive COVID-19, as defined under the primary endpoint, shown by gene sequencing to represent a variant not considered as a "variant of concern / interest" according to the CDC Variants Classification.
- First episode of PCR-positive moderate or severe COVID-19, as defined under the primary endpoint.
- ANY symptomatic SARS-CoV-2 infection, defined as: PCR-positive nasal swab and ≥ 1 of any of the symptoms considered qualifying for COVID-19 (Table 21).

Exploratory endpoints 2019nCoV-301:

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

Secondary endpoints 2019nCoV-302:

- First occurrence of virologically confirmed (by PCR to SARS-CoV-2), symptomatic *moderate or severe* COVID-19 with onset at least 7 days after second study vaccination (e.g., Day 28) in serologically negative (to SARS-CoV-2) adult participants at baseline until the endpoint-driven efficacy analysis is triggered by the occurrence of a prespecified number of blinded endpoints. (Defined as Key by the applicant).

- First occurrence of virologically confirmed (by PCR to SARS-CoV-2), symptomatic *severe* COVID-19 with onset at least 7 days after second study vaccination (e.g., Day 28) in serologically negative (to SARS-CoV-2) adult participants at baseline until the endpoint-driven efficacy analysis is triggered by the occurrence of a prespecified number of blinded endpoints.
- First occurrence of virologically confirmed (by PCR to SARS-CoV-2), symptomatic mild, moderate, or severe COVID-19, with onset at least 7 days after second study vaccination (e.g., Day 28) in adult participants *regardless of their serostatus at baseline.*
- First occurrence of COVID-19 requiring *hospitalisation, intensive care unit (ICU) admission or mechanical ventilation* linked to any virologically confirmed (by PCR to SARS-CoV-2) COVID-19 with onset at least 7 days after second study vaccination (e.g., Day 28) in adult participants *regardless* of their serostatus at baseline.

Exploratory endpoints 2019nCoV-302:

- First occurrence of virologically confirmed (by PCR to SARS-CoV-2), symptomatic mild, moderate, or severe COVID-19 with onset *at least 14 days after first study vaccination* (e.g., Day 14) in serologically negative (to SARS-CoV-2) adult participants at baseline until the endpoint-driven efficacy analysis is triggered by the occurrence of a prespecified number of blinded endpoints.
- Analysis of efficacy against symptomatic mild, moderate, or severe COVID-19, with onset from at least 7 days after second study vaccination (e.g., Day 28) in the initial set of vaccinations in seronegative adult participants by age (< 65 and ≥ 65), in racial and ethnic minorities, and in those with comorbid conditions.

Sample size

2019nCoV-301

The sample size for the original study design (described through protocol version 6.0) was driven by the total number of cases expected to achieve statistical significance for the primary efficacy endpoint; a total of up to approximately 30,000 participants ≥ 18 years of age would be enrolled to provide a target of 144 symptomatic PCR-confirmed SARS-CoV-2 infections.

Change during study: Given the mandate from the US Government that all adults would be eligible for an EUA vaccine as of 01 May 2021 and the decreasing prevalence of COVID-19 in the US during the timeframe for case accrual, the applicant identified that it would become extremely difficult to continue accruing COVID-19 cases. The applicant implemented the blinded crossover in Clinical Study 2019nCoV-301 on 20 April 2021 following accumulation of the median 2-month safety follow-up (targeted for 19 April 2021) and accumulation of cases for the efficacy analysis. With the implementation of the blinded crossover, the placebo-controlled portion of Clinical Study 2019nCoV-301 ended. In a protocol revision the two interim analyses for efficacy and futility that were planned, were removed. Only one analysis will be performed.

It was assumed as an example that with 75 events the minimum VE needed to demonstrate a lower bound of the confidence interval to be >30% would be VE 56%.

2019nCoV-302

This study is designed to enrol approximately 15,000 participants, who will be initially randomised 1:1 into the study vaccine groups. The sample size is driven by the total number of events expected to achieve statistical significance for the primary efficacy endpoint. A target of 100 mild, moderate, or severe COVID-19 cases was chosen to provide > 95% power for 70% or higher vaccine efficacy (VE).

A single interim analysis of efficacy will be conducted based on the accumulation of approximately 50% (50 events) of the total anticipated primary endpoints using Lan-DeMets alpha-spending function for Pocock boundary conditions, with a planned one-sided alpha of 0.01550 at 50% of the data and 0.01387 at the final analysis.

Randomisation and Blinding (masking)

In 2019nCoV-301, participants were randomised in a 2:1 ratio stratified by age group (18-64, ≥65 years of age), using randomly varying block sizes between 3 and 12. No formal stratification by site was conducted, however, at the time of randomisation of a participant at a site, a full block would be assigned to the site in order to maintain treatment assignment balance in the planned ratio at each site and allow for site and region effects to be assessed.

In 2019nCoV-302, participants were randomised to NVX-CoV2373 or placebo in a 1:1 ratio via block randomisation to NVX-CoV2373 or placebo, stratified by site and by age (<65 years, ≥ 65 years).

Both trials were designed as observer blinded trials. To maintain the blind, unblinded site personnel will manage study vaccine logistics, preparation, and administration so as to maintain the blind from the remainder of the site personnel and participants. The unblinded site personnel will not be involved in study-related assessments or have participant contact for data collection following study vaccine administration. It was made clear that for both studies blue-coloured translucent tape will be used on the syringe barrel to maintain the blind Clear rules surrounding potential unblinding were included in the protocols, however, communication between blinded and unblinded teams was possible. The DSMB was unblinded and reviewed the distribution of PCR+ cases over the trial arms during the study.

Statistical methods

The primary efficacy analysis set for both trials 2019nCoV-302 and 2019nCoV-301 was defined as the PP-EFF set, consisting of all randomised participants without major protocol deviations, who are seronegative (for SARS-CoV-2) at baseline and do not have a laboratory confirmed current SARS-CoV-2 infection with symptom onset up to 6 days after the second dose, and who have received both doses less than 45 days apart. Supportive efficacy analyses were defined in the intent-to-treat (ITT) (2019nCoV-302 study)/ full analysis set (FAS) (2019nCoV-301 study) sets including all participants who are randomised and have received at least 1 dose of study vaccine. For the 2019nCoV-301, a second per-protocol efficacy (PP-EFF-2) analysis set was defined followed the same method described in the PP-EFF population including all participants regardless of baseline serostatus.

For the *primary analysis* for both trials the VE was calculated as 100% x (1 – RR), where RR = Relative Risk calculated as ratio of incidence rates (SARS CoV-2 Rs with Matrix-M1 / Placebo), presented with 95% CI and an unadjusted one-sided p-value for testing H_0: VE ≤ 30%.

The primary endpoint was to be evaluated using a modified Poisson regression fitted to the occurrence of PCR confirmed COVID-19 disease (no infection, or one or more infections) with onset between 7 days after second study vaccination and end of study at 12 months (+15 days). The model included stratification factors and treatment group as fixed effects and robust error variances (Zou, 2004) as well as the natural log of the surveillance time as an offset. The explanatory variables included the treatment group and the stratification variables (age group (<65/ ≥65 years) and region [pooled sites] for study 302 only). The pooling of sites into regions will be determined and documented prior to breaking the blind for the 302 study. Where the model failed due sparsity of data, the Clopper Pearson approach, adjusted for surveillance time, was to be used. A sensitivity analysis was planned in both trials using a stratified Cox Proportional Hazard model with Efron's method of tie handling on the PP-EFF analysis.

A primary estimand was defined for 2019nCoV-302. This estimand seeks to understand efficacy during a surveillance period (7 days to 12 months after second vaccination), which starts after the vaccine is considered to have stimulated an immune response in adults naïve to SARS-CoV-2 infection (confirmed seronegative) who comply with the dosing schedule and do not start an infection prior to 7 days after second vaccination. A hypothetical strategy is used for unrelated deaths and significant protocol deviations (such as use of alternative vaccines and prohibited medications) so that interest lies in the hypothetical situation that these do not occur. As at the time of writing the protocol the estimand framework had not been fully implemented by all regulators globally, for pragmatic reasons, it was later decided to introduce the estimand framework, therefore it is not fully implemented.

No estimand was defined for 2019nCoV-301.

For 2019nCoV-302, the one-sided alpha was calculated using the Lan-DeMets alpha-spending for Pocock boundary conditions to account for the interim analysis.

For 2019nCoV-301, two formal interim analyses for efficacy and a futility were planned. However, the protocol was revised while the study was ongoing to perform one single primary analysis. This analysis was planned to be performed when the blinded crossover will be implemented, the timing has not been clarified.
For 2019nCoV-301, sensitivity analyses were planned to evaluate potential bias due to differential early unblinding: 1) Including additional potential covariates; 2) Using a Cox PH model with Inverse Probability of Censoring Weights (IPCW) (e.g., Robins 1993, Robins & Rotnitzky 1992, Robins & Finkelstein 2000); 2) Using an alternative Cox PH model with multiple-imputation using Zhao's method.

For 2019nCoV-302, data from the blinded crossover period as well as incomplete or unavailable data from the initial vaccination period was excluded from the efficacy analyses. For 2019nCoV-301, in general, missing data have been excluded, no imputations were conducted for missing efficacy data. A tipping point analysis was to be conducted for both trials to assess the impact of missing values on the primary conclusions.

Subgroup analyses were predefined for a range of subgroups based on age, sex, race and comorbidities, ethnicity and race.

The statistical analysis plan of 2019nCoV-301 includes pre-specification of how waning of efficacy will be studied, the statistical analysis plan of 2019nCoV-302 will be updated to include similar methodology.

Results

Recruitment

Study **2019nCoV-301** was initiated on 27 December 2020 (first participant screened) and completed enrolment on 18 February 2021 at 119 sites across the US and Mexico. The data cut-off date for the 60-day median safety follow-up analysis was 19 April 2021; collection of efficacy and safety follow-up data continued for events that began on or before 19 April 2021 through 01 June 2021. The study remains ongoing through approximately 2 years follow-up from the Day 21 injection.

Study **2019nCoV-302** was initiated on 28 September 2020 (first participant screened) and completed enrolment on 28 November 2020 at 33 sites across the UK. 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. All data were fully cleaned and locked on 26 January 2021 for the interim analysis and on 15 March 2021 for the final analysis. The study remains ongoing through approximately 1 year follow-up from the Day 21 injection.

Participant flow

Figure 4 . Study Participant flow 2019nCoV-301

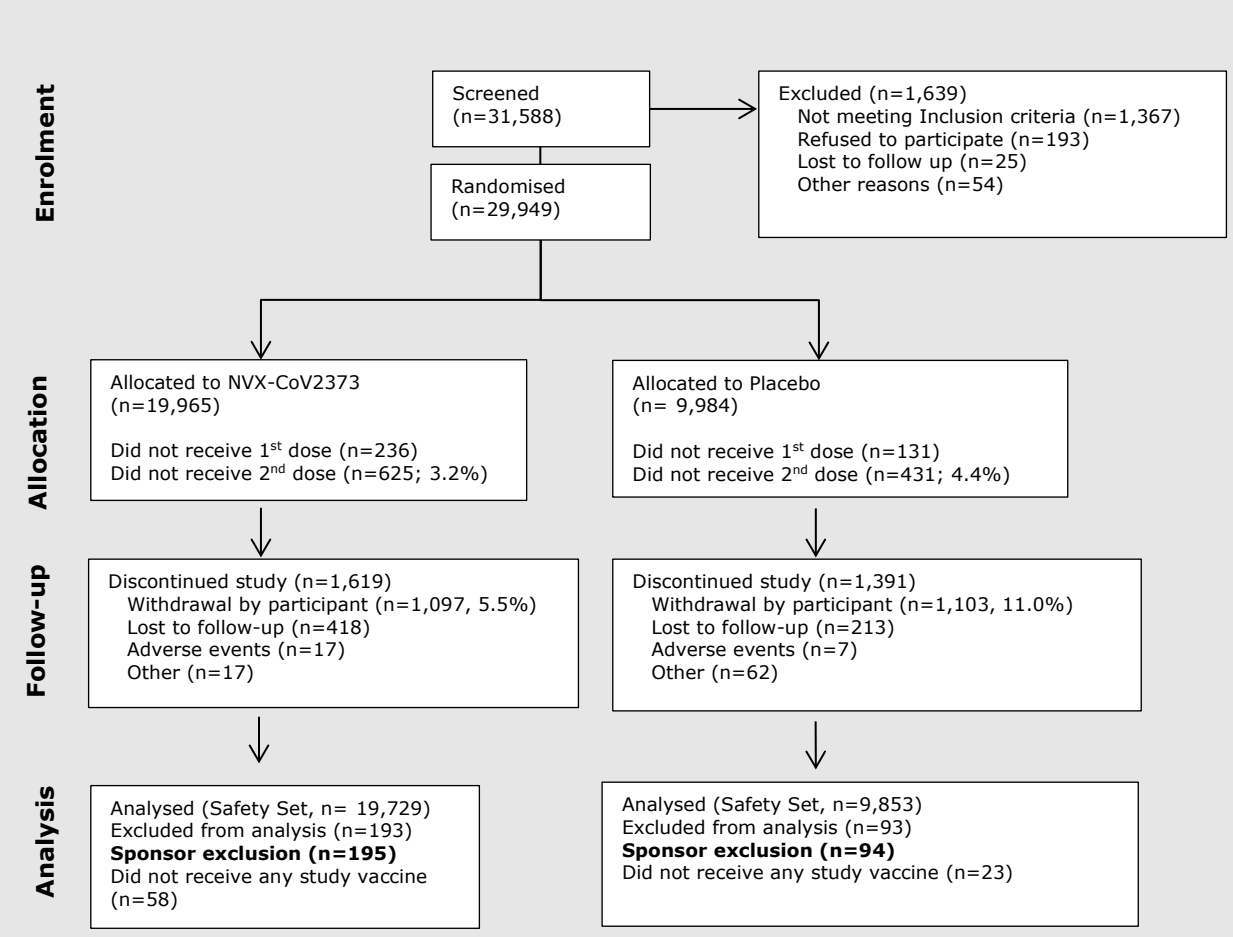
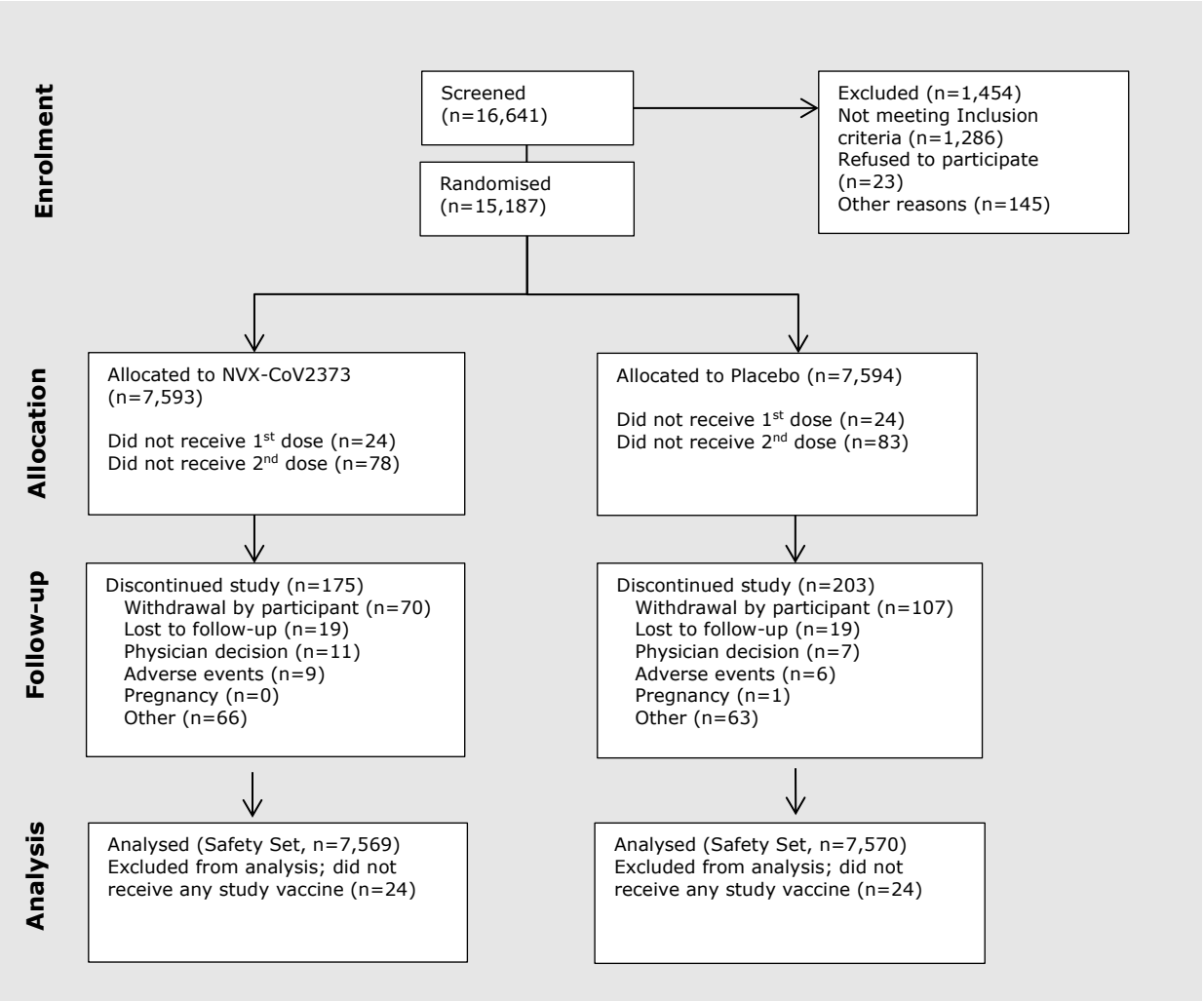


Figure 5 . Study Participant flow 2019nCoV-302



Conduct of the study

Protocol amendments

Both studies have gone through numerous changes.

Major change to protocol of study 2019nCoV-301 (final Protocol Version 9.0, 14 May 2021) included replacement of two interim analyses with a single efficacy analysis.

Initial major changes to the protocol of study 2019nCoV-302 (Version 4.0 (25 February 2021) included demoting a co-primary endpoint (protection against moderate-severe disease) to a secondary endpoint, and increasing recruitment.

Changes to the protocols are not expected to have impacted the robustness of the primary endpoint and overall study conclusions.

Baseline data

2019nCoV-301: Demographics and baseline characteristics of participants in the PP-EFF Analysis Set were well balanced between the NVX-CoV2373 and placebo groups. Median age was 47.0 years, with all participants ranging in age from 18 to 95 years. Approximately 11.8% of participants were ≥ 65 years of age, with 10.7% aged ≥ 65 to ≤ 74 years and 1.7% (n=405) aged ≥ 75 to ≤ 84 years. Approximately half the participants were male (51.8%), while the majority (75.9%) were White, and not of Hispanic or Latino origin (78.2%) and located in the United States (94.0%). Black or African Americans (11.0%), American Indians or Alaska Natives (6.2%), and Asians (4.4%) were well represented compared to the US population (US Census Bureau 2021). The majority of participants were overweight or obese (69.9%), with more than a third being obese (37.2%). Most participants (95.2%) were categorised as high-risk adults for acquiring or experiencing complications of COVID-19. A breakdown of underlying comorbidities at baseline in the study population is presented in Table 24. Baseline characteristics were similar between the PP-EFF analysis set and the safety population. Further, within the Safety population, most participants (93.5%) had a seronegative (based on anti-NP serology) and PCR negative (based on negative nasal swab PCR) baseline status prior to randomisation.

Table 15. Demographics and Baseline Characteristics (PP-EFF Analysis Set, 2019nCoV-301)

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)

Abbreviations: BMI = body mass index; max = maximum; min = minimum; NVX-CoV2373 = 5 µg SARS-CoV-2 rS with 50 µg Matrix-M1 adjuvant; PCR = polymerase chain reaction; PPE = personal protective equipment; SARS-CoV-2 rS = severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine; SD = standard deviation. High-risk adults were defined as 1) age ≥ 65 years with or without comorbidities and/or living or working conditions involving known frequent exposure to SARS-CoV-2 or to densely populated circumstances; 2) age > 65 years with comorbidities and/or living or working conditions involving known frequent exposure to SARS-CoV-2 or to densely populated circumstances.

2019nCoV-302: Demographics and baseline characteristics of participants in the PP-EFF Analysis Set were well balanced between the 2 study vaccine groups. Median age was 56.0 years, with all

participants ranging in age from 18 to 84 years. Approximately 28% of participants were ≥ 65 years of age, with 23.2% aged ≥ 65 to ≤ 74 years and around 4.1% (n=614) aged ≥ 75 to ≤ 84 years. Approximately half the participants were male (51.6%), and most were White (94.5%) and not of Hispanic or Latino origin (87.8%). All participants in the PP-Analysis set had a negative (or missing) baseline serostatus, and nearly 45% of participants were identified as having at least 1 comorbid condition reported as a medical history or had a screening BMI > 30 kg/m2. A breakdown of underlying comorbidities at baseline in the study population is presented in Table 24. Demographics and baseline characteristics of participants in the ITT Analysis Set were similar with the PP-EFF Analysis Set. Further, within the ITT population, most participants had a seronegative (based on anti-NP serology) or PCR negative (based on negative nasal swab PCR) baseline status prior to randomisation of 99.4% and 95.8%, respectively.

Table 16. Demographics and Baseline Characteristics (PP-EFF Analysis Set, 2019nCoV-302)

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)
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)

PP-EFF included all participants who received two doses of study vaccine wihtin 45 days apart, and did not have (symptom onset of) laboratory confirmed SARS-CoV-2 infection up to 6 days after the second study vaccination. 1. Baseline serostatus determined by serum IgG ELISA N-protein specific for SARS-CoV-2 rS. 2. Comorbid participants were those identified who had at least 1 comorbid condition reported as a medical history or had a screening BMI value greater than 30 kg/m2.

Table 17. Summary of Severe Obesity and Specified High-Risk Baseline Comorbidities from Medical History by Comorbidity Category and Preferred Terms for Clinical Studies 2019nCoV-301 and 2019nCoV-302 (Safety Analysis Set)

Severe Obesity and High-Risk Baseline Comorbidities (Comorbidity Category and Preferred Term)	2019nCoV-301		2019nCoV-302	
	NVX-CoV2373 N = 19729	Placebo N = 9853	NVX-CoV2373 N = 7569	Placebo N = 7570
Severe obesity (BMI ≥ 40 kg/m^2), n (%)	**1418 (7.2)**	**662 (6.7)**	**211 (2.8)**	**259 (3.4)**
Baseline comorbidities, n (%)				
Cardiac failure	**73 (0.4)**	**41 (0.4)**	**6 (< 0.1)**	**5 (< 0.1)**
Cardiac failure congestive	58 (0.3)	37 (0.4)	1 (< 0.1)	0
Cardiac failure	11 (0.1)	4 (< 0.1)	5 (< 0.1)	5 (< 0.1)
Cardiomyopathy	**26 (0.1)**	**8 (0.1)**	**3 (< 0.1)**	**1 (< 0.1)**
Cardiomyopathy	22 (0.1)	7 (0.1)	2 (< 0.1)	0
Chronic kidney disease	**131 (0.7)**	**58 (0.6)**	**37 (0.5)**	**43 (0.6)**
Chronic kidney disease	69 (0.3)	36 (0.4)	20 (0.3)	23 (0.3)
Nephropathy	17 (0.1)	6 (0.1)	0	0
Chronic liver disease	**118 (0.6)**	**63 (0.6)**	**42 (0.6)**	**31 (0.4)**
Hepatic steatosis	78 (0.4)	41 (0.4)	23 (0.3)	16 (0.2)
Non-alcoholic fatty liver disease	13 (0.1)	6 (0.1)	16 (0.2)	12 (0.2)
Hepatitis	11 (0.1)	4 (< 0.1)	2 (< 0.1)	1 (< 0.1)
Liver disorder	5 (< 0.1)	3 (< 0.1)	1 (< 0.1)	1 (< 0.1)
Chronic lung disease - other	**33 (0.2)**	**20 (0.2)**	**20 (0.3)**	**16 (0.2)**
Pulmonary mass	10 (0.1)	8 (0.1)	2 (< 0.1)	4 (< 0.1)
Pulmonary fibrosis	9 (< 0.1)	2 (< 0.1)	3 (< 0.1)	0
Pleurisy	1 (< 0.1)	1 (< 0.1)	8 (0.1)	5 (< 0.1)
Chronic lung disease - asthma	**1839 (9.3)**	**943 (9.6)**	**824 (10.9)**	**857 (11.3)**
Asthma	1706 (8.6)	865 (8.8)	765 (10.1)	811 (10.7)
Asthma exercise induced	87 (0.4)	52 (0.5)	14 (0.2)	10 (0.1)
Childhood asthma	25 (0.1)	20 (0.2)	41 (0.5)	32 (0.4)
Wheezing	12 (0.1)	2 (< 0.1)	5 (< 0.1)	3 (< 0.1)
Chronic lung disease - emphysema and chronic bronchitis	**304 (1.5)**	**188 (1.9)**	**78 (1.0)**	**82 (1.1)**
Chronic obstructive pulmonary disease	258 (1.3)	155 (1.6)	71 (0.9)	73 (1.0)
Bronchitis chronic	30 (0.2)	22 (0.2)	0	1 (< 0.1)
Emphysema	24 (0.1)	17 (0.2)	4 (< 0.1)	6 (< 0.1)
Congenital heart disease	**55 (0.3)**	**19 (0.2)**	**17 (0.2)**	**12 (0.2)**
Atrial septal defect	21 (0.1)	4 (< 0.1)	6 (< 0.1)	3 (< 0.1)
Bicuspid aortic valve	13 (0.1)	4 (< 0.1)	1 (< 0.1)	2 (< 0.1)
Ventricular septal defect	5 (< 0.1)	1 (< 0.1)	6 (< 0.1)	3 (< 0.1)
Coronary artery disease	**340 (1.7)**	**184 (1.9)**	**93 (1.2)**	**115 (1.5)**
Coronary artery disease	209 (1.1)	117 (1.2)	3 (< 0.1)	10 (0.1)
Myocardial infarction	164 (0.8)	76 (0.8)	37 (0.5)	49 (0.6)
Angina pectoris	31 (0.2)	22 (0.2)	22 (0.3)	33 (0.4)
Angina unstable	3 (< 0.1)	0	4 (< 0.1)	3 (< 0.1)

Table 17. Summary of Severe Obesity and Specified High-Risk Baseline Comorbidities from Medical History by Comorbidity Category and Preferred Terms for Clinical Studies 2019nCoV-301 and 2019nCoV-302 (Safety Analysis Set)

Severe Obesity and High-Risk Baseline Comorbidities (Comorbidity Category and Preferred Term)	2019nCoV-301		2019nCoV-302	
	NVX-CoV2373 N = 19729	Placebo N = 9853	NVX-CoV2373 N = 7569	Placebo N = 7570
Myocardial ischaemia	2 (< 0.1)	4 (< 0.1)	33 (0.4)	39 (0.5)
Cystic fibrosis	**2 (< 0.1)**	**1 (< 0.1)**	**0**	**0**
Cystic fibrosis	2 (< 0.1)	1 (< 0.1)	0	0
Diabetes mellitus type 1	**104 (0.5)**	**60 (0.6)**	**41 (0.5)**	**42 (0.6)**
Type 1 diabetes mellitus	104 (0.5)	60 (0.6)	41 (0.5)	42 (0.6)
Diabetes mellitus type 2	**1517 (7.7)**	**813 (8.3)**	**365 (4.8)**	**357 (4.7)**
Type 2 diabetes mellitus	1503 (7.6)	806 (8.2)	357 (4.7)	339 (4.5)
Diabetes mellitus	14 (0.1)	8 (0.1)	8 (0.1)	18 (0.2)
Gestational diabetes	**27 (0.1)**	**8 (0.1)**	**5 (< 0.1)**	**4 (< 0.1)**
Gestational diabetes	27 (0.1)	8 (0.1)	5 (< 0.1)	4 (< 0.1)
HIV infection	**159 (0.8)**	**64 (0.6)**	**8 (0.1)**	**14 (0.2)**
HIV infection	159 (0.8)	63 (0.6)	8 (0.1)	14 (0.2)

Abbreviations: BMI = body mass index; MedDRA = Medical Dictionary for Regulatory Activities; 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.

Notes: Medical History is coded using MedDRA, Version 23.1.

Source: Tables Adhoc EMA Q29_a_1 [2019nCoV-301] and Table 14.1.5.3_EMA [2019nCoV-302] in EMA_03 Nov_Q40 Attachment.

Numbers analysed

2019nCoV-301

Of the 29,949 participants randomised, 29,949 (100%) were in the ITT Analysis Set, 29,582 (98.8%) were in the FAS, and 29,582 (98.8%) were in the Safety Analysis Set. The PP-EFF Analysis Set included 25,452 (85.0%) randomised participants, with 17,312 (86.7%) in the NVX-CoV2373 group and 8,140 (81.5%) in the placebo group. Overall, data analysis sets were generally well balanced between the 2 study vaccine groups.

Table 18. Analysis Sets (All Randomised Participants, 2019nCoV-301)

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)

Abbreviations: FAS = Full Analysis Set; ITT = Intent-to-Treat; NVX-CoV2373 = 5 µg SARS-CoV-2 rS with 50 µg Matrix-M1 adjuvant; PP-EFF = Per-Protocol Efficacy; SARS-CoV-2 rS = severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine.

Source: T14.1.2

The FAS excluded 289 (1.0%) participants (195 [1.0%] in the NVX-CoV2373 group and 94 [0.9%] in the placebo group), predominantly due to the exclusion of all participants from Site US151 and 14 participants from Site 076. Site US151 is being terminated from participating in Clinical Study 2019nCoV-301 for critical and major observations identified during a for-cause audit regarding the

Principal Investigator's lack of compliance with regulations in place. There were 280 subjects randomised at this site with approximately 248 subjects ongoing.

Study discontinuation occurred in 1,619 (8.1%) in the NVX-CoV2373 group and 1,391 (13.9%) in the placebo group, most frequently due to withdrawal by participant (NVX-CoV2373 5.5%, placebo 11%).

Fourteen participants from Site US076 were excluded due to having received NVX-CoV2373 from single-dose vials rather than the multi-dose vial.

The PP-EFF Analysis Set excluded 4,497 (15.0%) participants (2,653 [13.3%] in the NVX-CoV2373 group and 1,844 [18.5%] in the placebo group). The most frequent (incidence > 2.00% in any vaccine group) reasons for exclusion were baseline positive anti-NP result (5.6%), censored prior to observation period (4.5%), did not complete vaccination schedule (4.0%), and protocol deviation (3.3%).

Approximately 18% of participants were unblinded to study treatment assignment during the course of the study. The most frequent reason was to receive an authorised vaccine. There was an obvious 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. It is speculated that this difference may reflect the perception of study participants based on their reactogenicity symptoms or serologic testing outside of the study. No obvious association between reactogenicity profile and request for unblinding has been observed (supporting tables not shown). Data on serologic testing outside of the study has not been collected. Further it is noted that a larger proportion of participants in the placebo group did not receive their second dose compared to the participants in NVX-CoV2373 group (3.2% vs 4.4%). Also, a larger proportion of participants in the placebo group discontinued the study (8.1% vs 13.9%).

2019nCoV-302

Of the 15,187 participants randomised, 15,139 (99.7%) were in the ITT and Safety Analysis Sets with 7,569 in the NVX-CoV2373 group and 7,570 in the placebo group (Table 26).

The PP-EFF Analysis Set included 14,039 (92.4%) randomised participants, with 7,020 in the NVX-CoV2373 group and 7,019 in the placebo group. A total of 1,100 (7.3%) participants were excluded from the PP-EFF Analysis Set, the most frequent (incidence > 1.0%) reasons for exclusion from the PP-EFF Analysis Set were positive serostatus before 7 days after second vaccination, missed 1 dose of study vaccine, and positive PCR test before 7 days after second vaccination.

Approximately one-third of participants (34.6%) were unblinded to study vaccine assignment during the course of the study). The most frequent reason was receipt of an authorised vaccine. Most (98.2%) unblinded participants continued to be followed up in the study.

Table 19. Analysis Sets (All Randomised Subjects Analysis Set 2019nCoV-302)

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)

Outcomes and estimation

Primary Endpoint

2019nCoV-301

After the protocol revision one single primary analysis was performed.

For the primary analysis of the primary endpoint, there were 77 cases. Of these cases, 14 (0.1%) were in the NVX-CoV2373 group and 63 (0.8%) were in the placebo group; all 14 cases in the NVX-CoV2373 group were mild in severity; 59 cases in the placebo group were mild or moderate and 5 were severe. There were 3 hospitalisations due to COVID-19 among the 77 per-protocol COVID-19 cases in this study. The resultant VE was **90.40% (95% CI: 82.88, 94.62),** with a p-value of < 0.001 confirming the lower bound of the two-sided 95% CI > 30% and meeting the prespecified study success criterion of the study.

2019nCoV-302

Confirmatory interim analysis

There were 62 cases accrued for the prespecified interim analysis of the primary endpoint, with 6 (<0.1%) in the NVX-CoV2373 group and 56 (0.8%) in the placebo group. The resultant estimated VE was 89.3% (alpha-adjusted 96.9% CI: 73.0, 95.8; p < 0.0001), with an alpha-adjusted LBCI > 30% meeting the prespecified study success criterion.

Final primary efficacy analysis

There were 106 cases for the final prespecified analysis of the primary endpoint, with 10 (0.1%) in the NVX-CoV2373 group and 96 (1.4%) in the placebo group. All but 4 cases were mild or moderate in severity, with all 4 severe cases, including 1 hospitalisation and 1 person with a pulmonary embolism, occurring in the placebo group. The resultant estimated VE was **89.7% (95% CI: 80.2, 94.6; p < 0.001)**, with an LBCI > 30% meeting the prespecified study success criterion. These findings confirmed the results of the interim analysis of the primary endpoint.

Secondary Endpoints 2019nCoV-301

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

Viral genetic sequences were available for 54 of 77 primary endpoint cases in the PP-EFF.

Ten of these cases (0 in the NVX-CoV2373 group and 10 [0.1%] in the placebo group) were prototype-like and did not contain any of the mutations that would identify them as a VOC/VOI, including 3 that were moderate or severe. Resequencing of the PCR-positive cases that had not initially yielded sequencing results resulted in an additional 3 mild cases with non-VOC/VOI sequences in the placebo group (for a total of 13 [0.2%] cases).

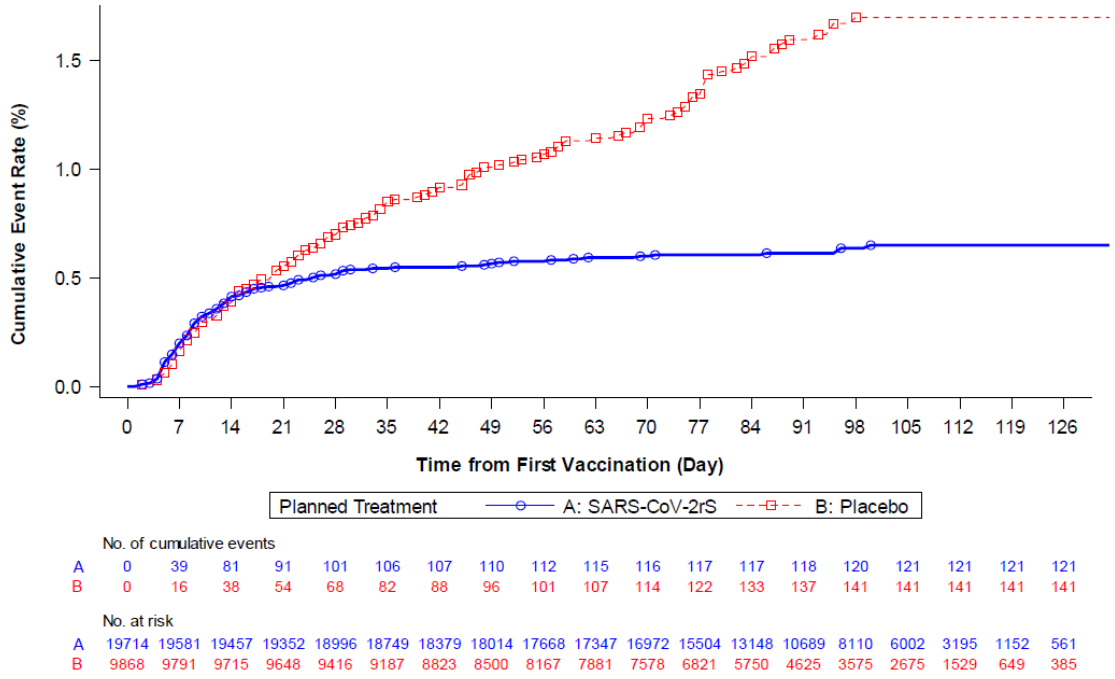
The VE of NVX-CoV2373 to prevent symptomatic mild, moderate, or severe COVID-19 due to a SARS-CoV-2 variant not considered as a VOC/VOI in serologically negative (to SARS-CoV-2) adult participants was 100% (95% CI: 80.8, 100; $p < 0.001$), and 100% (95% CI: 85.8, 100) with the 3 additional sequenced cases.

- *First episode of PCR-positive moderate or severe COVID-19, as defined under the primary endpoint.*

There were 14 cases of PCR-confirmed symptomatic **moderate or severe COVID-19** with onset from at least 7 days after second vaccination accrued for this analysis, with 0 in the NVX-CoV2373 group and 14 (0.2%) in the placebo group. The resultant VE of NVX-CoV2373 to prevent symptomatic moderate or severe COVID-19 in baseline seronegative (to-SARS-CoV-2) adult participants was 100% (95% CI: 87.0, 100).

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

Of the 276 cases with onset from first vaccination, 14 were virologically confirmed with at least one COVID-19 symptom and 262 were mild, moderate, or severe COVID-19. Of the 262 PCR-positive cases of mild, moderate, or severe COVID-19, 203 had sequence data available as summarised. Of these, 82 were identified as VOC/VOI clades, lineages, or variants of SARS-CoV-2. The most common VOC were B.1.1.7 (Alpha), which occurred in 46 cases. During the period of case accrual, no cases of infection due to the B.1.617.2 (Delta) variant were identified.



Source: F14.2.1.3.6

Figure 6 Cumulative Incidence Curve of PCR-Confirmed Mild, Moderate, or Severe COVID-19 Disease with Onset from First Vaccination in Adult Participants Who Received at Least 1 Dose of Study Vaccine Regardless of Baseline Serostatus (Full Analysis Set, 2019nCoV-301)

In the PP-EFF Analysis Set, 44 cases (6 in the NVX-CoV2373 group and 38 in the placebo group) had mutations that would identify them as a VOC or VOI. In the NVX-CoV2373 group, all 6 cases were mild in severity; in the placebo group, 9 of 38 cases were moderate or severe. The resultant VE of NVX-CoV2373 to prevent symptomatic mild, moderate, or severe COVID-19 due to a SARS-CoV-2 variant considered a VOC or VOI in baseline seronegative adult participants was 93. 2% (95% CI: 83.97, 97.1), with a p-value < 0.001 confirming the lower bound of the one-sided 95% CI > 0%.

Secondary Endpoints 2019nCoV-302:

- *Efficacy by strain (PP-EFF analysis set)*

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.

- *Protection against symptomatic moderate or severe COVID-19 with onset at least 7 days after second study vaccination (e.g., Day 28) in baseline seronegative subjects. (defined as key by the applicant)*

There were 77 out of 106 cases of PCR-confirmed symptomatic moderate or severe COVID-19 with onset from at least 7 days after second vaccination, with 9 (0.1%) in the NVX-CoV2373 group and 68 (1.0%) in the placebo group. The resultant estimated VE of NVX-CoV2373 to prevent symptomatic moderate or severe COVID-19 in baseline seronegative (to SARS-CoV- 2) adult participants was 86.9% (95% CI: 73.7, 93.5).

- *Protection against symptomatic severe COVID-19 with onset at least 7 days after second study vaccination (e.g., Day 28) in baseline seronegative subjects.*

At the time of the final analysis there were 4 cases classified as severe in the placebo group and none in the NVX-CoV2373 group occurring at least 7 days after the second dose in serologically negative adult participants in the PP-EFF analysis set.

- *Protection against hospitalisation, intensive care unit (ICU) admission or mechanical ventilation linked to any virologically confirmed COVID-19 with onset at least 7 days after second study vaccination (e.g., Day 28) in adult participants regardless of their serostatus at baseline.*

There were 2 cases of PCR-confirmed symptomatic moderate or severe COVID-19 requiring hospitalisation, ICU admission, or mechanical ventilation with onset from at least 7 days after second vaccination in serologically negative adult participants, with 0 in the NVX-CoV2373 group and 2 in the placebo group.

- *Protection against COVID-19 in adults regardless of baseline serostatus*

There were 107 cases of PCR-confirmed symptomatic mild, moderate, or severe COVID-19 with an onset from at least 7 days after second vaccination in participants regardless of baseline serostatus, with 10 (0.1%) in the NVX-CoV2373 group and 97 (1.3%) in the placebo group. Vaccine efficacy of NVX-CoV2373 to prevent symptomatic mild, moderate, or severe COVID-19 in adult participants regardless of baseline serostatus was estimated to be 89.8% (95% CI: 80.5, 94.7).

There were 183 cases of PCR-confirmed mild, moderate, or severe COVID-19 with onset from first vaccination through the data cut-off date of the final analysis of the primary endpoint. PCR-confirmed COVID-19 occurred in 42 (0.6%) participants (1.742/1,000 person-years) in the NVX-CoV2373 group and 141 (1.9%) cases (1.728/1,000 person-years) in the placebo group at the time of the final analysis of the primary endpoint (median surveillance time 85 days), with no participant having more than 1 episode of COVID-19. The resultant estimated VE of NVX-CoV2373 to prevent symptomatic mild, moderate, or severe COVID-19 from first vaccination in adults regardless of baseline serostatus was 70.5% (95% CI: 58.0, 79.6; Clopper-Pearson method). The vaccine efficacy against confirmed mild, moderate or severe COVID-19 with onset after first vaccination in adults regardless of baseline serostatus is shown in Table 27 for different time periods.

Table 20. Vaccine Efficacy against PCR-Confirmed Symptomatic Mild, Moderate, or Severe COVID-19 with Onset from First Vaccination in Adult Participants Regardless of Baseline Serostatus (ITT Analysis Set, 2019nCoV-302)

Surveillance Period	NVX-CoV2373 N = 7569			Placebo N = 7570			Vaccine Efficacy	95% CI[1]
	n1	n2	Total Surveillance Time in 1000 person-years[2]	n1	n2	Total Surveillance Time in 1000 person-years[2]		
First COVID-19 occurrence[3] after Dose 1 (Day 0+)	42	7566	1.742	141	7565	1.728	70.5	58.0, 79.6
Day 0 to Day 6	8	7566	0.145	5	7565	0.145	-60.0	-521.4, 53.9
Day 7 to Day 13	13	7555	0.145	11	7554	0.145	-18.2	-191.3, 51.1
Day 14 to Day 20	5	7541	0.144	11	7540	0.144	54.6	-41.9, 87.6
Day 21 to Day 28	2	7526	0.144	13	7520	0.144	84.6	32.1, 98.3
≥ Day 7	34	7555	1.597	136	7554	1.583	75.2	63.7, 83.5
≥ Day 14	21	7541	1.452	125	7540	1.438	83.4	73.4, 90.1
≥ Day 21	16	7526	1.308	114	7520	1.294	86.1	76.5, 92.3
≥ Day 28	14	7483	1.164	101	7475	1.150	86.3	75.9, 92.8

1. CI for vaccine efficacy was derived from the Clopper-Pearson method. The 95% CI was calculated using the Clopper-Pearson exact binomial method adjusted for the total surveillance time.
2. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint.
3. Event = first occurrence of PCR-confirmed mild, moderate or severe COVID-19 with onset from first vaccination within the surveillance period.

The cumulative incidence curve of PCR confirmed COVID-19 cases over time since first vaccination in both groups is displayed in Figure 10 below.

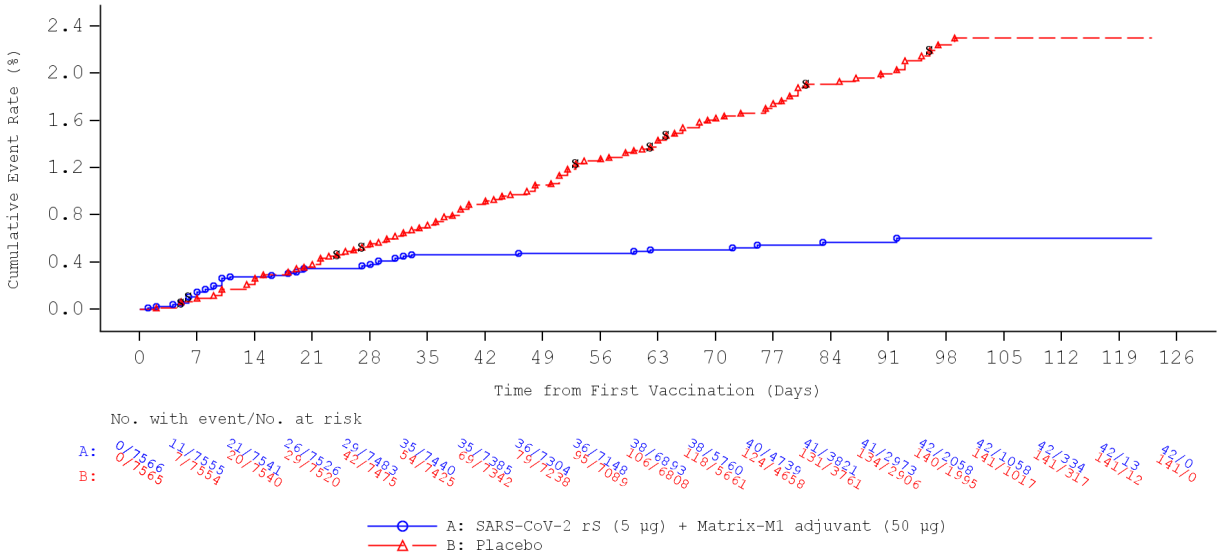


Figure 7 . Cumulative Incidence Curve of PCR-Confirmed Symptomatic Mild, Moderate, or Severe COVID-19 with Onset from First Vaccination in Adult Participants Regardless of Baseline Serostatus (ITT Analysis Set, 2019nCoV-302)

Vaccine efficacy adjusted for surveillance time was 24.0% (-38.1, 58.1), 42.8% (-16.2, 71.9) and 57.1% (-18.8, 86.5) when onset was from at least 7 days, 10 days and 14 days after first vaccination and an observation period up to the second vaccination. The median duration of illness was 12.5 days in the vaccine group and 13.0 days in the placebo group.

Ancillary analyses

Subgroup analyses 2019nCoV-301

The VEs of NVX-CoV2373 at the time of the final analysis of the primary endpoint, for which an adequate number of cases were identified, were consistent across major demographic and baseline characteristic subgroups and are shown in the tabled overview below. The relatively lower VE of 67.3% (95% CI: 18.7, 86.8) for participants of Hispanic or Latino ethnicity, may reflect social or economic characteristics in the locations where the participants were enrolled. Immunogenicity, measured by anti-S IgG ELISA assay, neutralising antibody titers, and hACE2 receptor binding inhibition titers at baseline and Day 35, demonstrated that the immune responses in Hispanic/Latino participants were equivalent (although uniformly slightly higher) to those in non-Hispanic/Latino participants.

Table 21 Subgroup Analyses 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)

Parameter	Number of Events[1]/Subgroup		Vaccine Efficacy (95% CI)	P-Value[2]
	NVX-CoV2373	Placebo		
Final analysis of the primary endpoint	**14/17312 (0.1)**	**63/8140 (0.8)**	**90.40% (82.88, 94.62)[3]**	**< 0.001**
Subgroup: Age				
Participants 18 to ≤ 64 years of age	12/15264 (0.1)	61/7194 (0.8)	91.50% (84.21, 95.42)[3]	< 0.001
Participants ≥ 65 years of age	2/2048 (0.1)	2/946 (0.2)	57.46% (-486.91, 96.92)[4]	0.381
Subgroup: Sex				
Male	5/9050 (0.1)	23/4131 (0.6)	90.89% (76.03, 96.54)[3]	< 0.001
Female	9/8262 (0.1)	40/4009 (1.0)	89.99% (79.36, 95.14)[3]	< 0.001
Subgroup: Race (summary)				
White	12/13140 (0.1)	48/6184 (0.8)	89.37% (79.99, 94.35)[3]	< 0.001
Non-White	2/4068 (< 0.1)	14/1911 (0.7)	93.57% (71.68, 98.54)[3]	< 0.001
Subgroup: Race (individual)				
White	12/13140 (0.1)	48/6184 (0.8)	89.37% (79.99, 94.35)[3]	< 0.001
Black or African American	0/1893 (0.0)	7/905 (0.8)	100.00% (67.86, 100.00)[4]	0.007
American Indian or Alaska Native	0/1074 (0.0)	2/498 (0.4)	100.00% (-143.63, 100.00)[4]	0.097
Asian	0/761 (0.0)	5/366 (1.4)	100.00% (52.81, 100.00)[4]	0.025
Native Hawaiian or Other Pacific Islander	0/47 (0.0)	0/10 (0.0)	NE[4]	NE
Multiple	2/293 (0.7)	0/132 (0.0)	NE[4]	NE
Not reported/unknown	0/104 (0.0)	1/45 (2.2)	100.00% (-1549.64, 100.00)[4]	0.196
Subgroup: Ethnicity				
Hispanic or Latino	8/3733 (0.2)	11/1751 (0.6)	67.28% (18.65, 86.84)[3]	0.008
Not Hispanic or Latino	6/13538 (< 0.1)	52/6379 (0.8)	95.08% (88.54, 97.89)[3]	< 0.001
Subgroup: Country				
US	14/16294 (0.1)	62/7638 (0.8)	90.36% (82.78, 94.60)[3]	< 0.001
Mexico	0/1018 (0.0)	1/502 (0.2)	100.00% (-1791.89, 100.00)[4]	0.166
Subgroup: Comorbidity status[5]				
Yes	7/8109 (0.1)	34/3910 (0.9)	90.76% (79.16, 95.90)[3]	< 0.001
No	7/9203 (0.1)	29/4230 (0.7)	89.94% (77.05, 95.59)[3]	< 0.001
Subgroup: High-risk status[6]				
Yes	13/16493 (0.1)	62/7737 (0.8)	90.96% (83.57, 95.03)[3]	< 0.001
No	1/819 (0.1)	1/403 (0.2)	55.08% (-3426.09, 99.43)[4]	0.443

Abbreviations: BMI = body mass index; CI = confidence interval; COVID-19 = coronavirus disease 2019; NVX-CoV2373 = 5 µg SARS-CoV-2 rS with 50 µg Matrix-M1 adjuvant; PCR = polymerase chain reaction; PP = Per-Protocol; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SARS-CoV-2 rS = severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine.

1. Event = First occurrence of PCR-confirmed mild, moderate or severe COVID-19 with onset from 7 days after the second vaccination within the surveillance period.
2. P-value corresponded to a one-sided hypothesis test with significance level 0.025. If the VE p-value < 0.025, then reject H0: VE ≤ 0%.
3. Based on Log-linear model of occurrence using modified Poisson regression with logarithmic link function, treatment group and strata (age-group and pooled region) as fixed effects and robust error variance [Zou 2004] fitted separately to each subgroup.
4. In the event when there were zero cases in either vaccine group or the total number of cases in both vaccine groups combined < 5, VE and 95% CI were estimated with 1 – ratio of incidence rates using the exact method conditional on the total number of cases. NE = not estimable in the event the test for exact binomial proportion cannot be conducted.
5. Comorbidities: Obesity (BMI ≥ 30 kg/m^2), chronic kidney disease, chronic lung disease, cardiovascular disease, diabetes mellitus type 2.
6. High-risk adults were defined as 1) age ≥ 65 years with or without comorbidities and/or living or working conditions involving known frequent exposure to SARS-CoV-2 or to densely populated circumstances; 2) age > 65 years with comorbidities and/or living or working conditions involving known frequent exposure to SARS-CoV-2 or to densely populated circumstances.

Source: T14.2.1.1.2, T14.2.1.1.4.1, T14.2.1.1.4.2, T14.2.1.1.4.3.1, T14.2.1.1.4.3.3, T14.2.1.1.4.4, T14.2.1.1.4.5, T14.2.1.1.4.6, T14.2.1.1.4.7

Subgroup analyses 2019nCoV-302

The VEs of NVX-CoV2373 at the time of the final analysis of the primary endpoint, for which an adequate number of cases were identified, were consistent across major demographic and baseline characteristic subgroups (Table 29). Vaccine efficacy was comparable between males (88.2%; 95% CI: 70.2, 95.3) and females (91.0%; 95% CI: 77.3, 96.4).

Table 22 Subgroup Analyses of Vaccine Efficacy against PCR-Confirmed Symptomatic (PP-EFF Analysis Set, 2019nCoV-302)

Subgroup	Number of Events[1]/Subgroup		Vaccine Efficacy (95% CI)
	NVX-CoV2373 N = 7020	Placebo N = 7019	
Final analysis of the primary endpoint	**10/7020**	**96/7019**	**89.7% (80.2, 94.6)**
Age strata			
Participants 18 to 64 years of age	9/5067	87/5062	89.8% (79.7, 94.9)[2]
Participants 65 to 84 years of age	1/1953	9/1957	88.9% (20.2, 99.7)[3]
Race			
White	8/6625	85/6635	90.7% (80.8, 95.5)[2]
Non-White (ethnic minorities)	2/232	6/238	66.3% (-88.4, 96.7)[3]
Non-White (ethnic minorities) and multiple	2/302	8/297	75.7% (-21.6, 97.5)[3]
Baseline comorbidities[4]			
Presence	3/3117	33/3143	90.9% (70.4, 97.2)[2]
Absence	7/3903	63/3876	89.1% (76.2, 95.0)[2]

Abbreviations: BMI = body mass index; CI = confidence interval; COVID-19 = coronavirus disease 2019; NVXCoV2373 = 5 µg SARS-CoV-2 rS with 50 µg Matrix-M1 adjuvant; PCR = polymerase chain reaction; PP = Per- Protocol; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SARS-CoV-2 rS = severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine.

1. Event = First occurrence of PCR-confirmed mild, moderate or severe COVID-19 with onset from 7 days after the second vaccination within the surveillance period.
2. Based on Log-linear model of occurrence using modified Poisson regression with logarithmic link function, treatment group and strata (age-group and pooled region) as fixed effects and robust error variance [Zou 2004].
3. The Clopper-Pearson model replaced the log-linear model using the modified Poisson regression because few events were observed in at least 1 of the study vaccine groups (or at least 1 stratum) and Poisson regression analysis failed to converge. The 95% CIs calculated using the Clopper-Pearson exact binomial method adjusted for the total surveillance time.
4. Comorbid participants were those who had at least 1 of the comorbid conditions reported as a medical history or had a screening BMI > 30 kg/m2.

Potential impact on unblinding in studies 2019nCoV-301 and 2019nCoV-302

To assess whether potential awareness of treatment allocation in study 2019nCoV-301 had an impact on the reporting of symptoms and collection of endpoint data, the applicant was requested to provide information on the number of acute illness visits, number of swabs taken and percentage positive and negative tests. A summarising overview* is displayed below:

	COV301		**COV302**	
	NVX-COV2373	Placebo	NVX-COV2373	Placebo
N Participants	19965	9984	7569	7569
Acute illness visit	**1653 (8.3%)**	**866 (8.7%)**	**2127 (28%)**	**2149 (28%)**
Nr of swabs taken	5933	3115	1672	1898
% of participants with swab taken, assuming 4 swabs/person	7.4%	7.8%	5.5%	6.3%
Positive test N	468	497	150	453
% positive test	**7.9%**	**16%**	**9.0%**	**23.9%**
Negative test	5465	2618	1507	1426
% participants with negative test, assuming 4 swabs/person	**6.8%**	**6.6%**	**5.0%**	**4.7%**

*Calculations of the percentages have been performed by the assessment team. Up to 4 tests could have been taken per person, although not all participants had in fact taken 4 tests. This number was considered for the calculations.

There were no major differences in acute illness visits between the trial arms. The percentage of participants randomised who were tested and had a negative test result was comparable over the study arms, while the percentage positive tests was different.

Summary of main efficacy results

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

Table 23 Summary of efficacy for Study 2019nCoV-301

Title: 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-M1 adjuvant in adult participants ≥ 18 years with a paediatric expansion in adolescents (12 to < 18 years). 2019nCoV-301: Interim report		
Study identifier	Protocol 2019nCoV-301	
Design	The study is a phase 3, randomized 2:1, observer-blinded, placebo-controlled, multi-centre (US and Mexico) trial to evaluate the efficacy, safety and immunogenicity of the vaccine NVX-CoV2373 containing 5µg SARS-CoV-2 rS with 50 µg Matrix-M1 adjuvant	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Screening period 30 days Main phase: 3 weeks Follow up 24 months
Hypothesis	Superiority	

Treatments groups	NVX-CoV2373		2 doses of SARS-CoV-2rS (5 µg) Matrix-M1 (50 µg) in 0.5 ml 21 days apart. N = 19965
	Placebo		0.5 ml saline N = 9984
Endpoints and definitions	Primary endpoint	To prevent confirmed COVID-19 starting 7 days after Dose 2	VE will be estimated as 1 - RR (NVX-CoV2373 vs placebo). A Poisson regression model utilizing robust error variance and an offset to account for variable follow-up time was used to estimate the relative risk (RR) and VE with cases counted starting 7 days after the second dose of IP.
	Key secondary endpoint	To prevent PCR-confirmed COVID-19 due to a SARS-CoV-2 variant not considered as a VOC or VOI as classified by gene sequencing	The analysis approach used the same approach as the primary objective using a one-sided alpha of 0.025 at the primary analysis against the same null hypothesis as the primary efficacy endpoint, H0: VE ≤ 30% (RR ≥ 0.70).
	Other secondary endpoint	To prevent PCR-Confirmed Moderate or Severe COVID-19 with Onset from at Least 7 Days after Second Vaccination	The analysis approach used the same approach as the primary objective.
Database lock	Interim efficacy analysis: 31 May 2021		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	The Per-Protocol Efficacy (PP-EFF) Analysis Set included all participants who received the full prescribed regimen of trial vaccine and had no major protocol deviations that occurred before the first COVID-19 positive episode and were determined to affect the efficacy outcomes, including baseline SARS-CoV-2 seropositivity or nasal swab PCR -positivity. Participants who were unblinded with an intention to receive other COVID-19 vaccines were censored at the time of unblinding. Although the study enrolled participants regardless of SARS-CoV-2 serologic status at the time of initial vaccination, any participants with confirmed infection or prior infection (due to SARS-CoV-2 at baseline, by nasal swab PCR or serology assessed by Anti-Nucleocapsid, were excluded from the PP-EFF population. PP-EFF was the primary set for all efficacy endpoints.			
Descriptive statistics and estimate variability	Treatment group	NVX-CoV2373	Placebo	
	Number of subjects (PP-EFF set)	17312	8140	
	Cases n (%)	14	63	

	Incidence rate per year in 1000 people	(0.1) 3.26	(0.8) 34.01	
	Confidence interval	1.55, 6.89	20.70, 55.87	

Effect estimate per comparison	Primary endpoint	Comparison groups	NVX-CoV2373 to placebo 17312/8140
		VE: 1 - hazard ratio (NVX-CoV2373 vs. placebo) Cox proportional hazard model	90.4 90.4
		95% CI Cox proportional hazard model	82.9, 94.6 82.9, 94.6
		P-value (H_0: VE ≤ 30%)	< 0.001 < 0.001
	Key secondary endpoint	Comparison groups	NVX-CoV2373 to placebo 17312/8140
		VE: 1 - hazard ratio (NVX-CoV2373 vs. placebo)	100%
		95% CI	80.8, 100.0
		P-value	< 0.001
	Secondary endpoint (as mentioned above)	Comparison groups	NVX-CoV2373 to placebo 17312/8140
		VE: 1 - hazard ratio (NVX-CoV2373 vs. placebo)	100%

		95% CI	87.0, 100.0
		P-value	NE

Table 24 Summary of efficacy for Study 2019nCoV-302

Title: A phase 3, randomised, observer-blinded, placebo-controlled trial to evaluate efficacy and safety of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine (SARS-CoV-2 rS) with Matrix-M1 adjuvant in adult participants 18-84 years of age in the United Kingdom			
Study identifier	2019nCoV-302		
Design	Phase 3, multicenter, randomized 1:1, observer-blinded, placebo-controlled study evaluating the efficacy, safety, and immunogenicity of 5 µg SARS-CoV-2 rS with 50 µg Matrix-M1 adjuvant administered twice 21 days apart in adult participants 18 to 84 years of age (inclusive) conducted at 33 sites in the UK.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		35 (+7) Days Day -30 to Day 0 1 year
Hypothesis	Superiority		
Treatments groups	NVX-CoV2373		2 doses of SARS-CoV-2 rS (5µg)+Matrix-M1 (50µg) in 0.5 ml 21 days apart N=7593
	Placebo		0.5 ml saline placebo N=7595
Endpoints and definitions	Primary endpoint	Prevention of COVID-19 in serologically negative adults	Vaccine efficacy measured as VE (%) =100 × (1-RR) in SARS-CoV-2-serologically negative adults who received both the first study vaccination and the second study vaccination after 3 weeks. RR was the relative risk (SARS-CoV-2 Matrix-M1/placebo) of the first occurrence of PCR-confirmed mild, moderate, or severe COVID-19 with onset during a surveillance period from at least 7 days after second study vaccination
	Secondary endpoint	Prevention of moderate or severe COVID-19 in serologically negative adults	Vaccine efficacy measured as VE (%) =100 × (1-RR) in SARS-CoV-2-serologically negative adults who received both the first study vaccination and the second study vaccination after 3 weeks. RR was the relative risk (SARS-CoV-2 Matrix-M1/placebo) of the first occurrence of

			PCR-confirmed moderate or severe COVID-19 with onset during a surveillance period from at least 7 days after second study vaccination
Database lock	Data cutoff date for the interim report 26.2.2021		

Results and Analysis

Analysis description	**Primary – Interim & Final - Analysis**			
Analysis population and time point description	The Per-Protocol Efficacy (PP-EFF) Analysis Set including baseline seronegative participants who received both doses of study vaccine (SARS-CoV-2 rS with Matrix-M1 adjuvant or placebo) and had no major protocol deviations that occurred before the first COVID-19 episode affecting the primary efficacy outcome as assessed by the sponsor prior to unblinding. All analyses of the PP-EFF population also excluded any illness episodes with positive SARS-CoV-2 by any validated PCR or antibody test occurring 6 days or less after second vaccination (eg, Day 28).			
Descriptive statistics and estimate variability Interim analysis	Treatment group	NVX-CoV2373	Placebo	
	Number of subjects (PP-EFF set)	7016	7033	
	Cases (%) Incidence rate per year in 1000 people 95% CI	6 (<0.1) 5.06 1.94, 13.18	56 (0.8) 47.30 28.72, 77.88	
Final analysis	Number of subjects (PP-EFF set)	7020	7019	
	Cases (%) Incidence rate per year in 1000 people 95% CI	10 (0.1) 6.53 3.32, 1285	96 (1.4) 63.43 45.19, 89.03	
Effect estimates per comparison	Primary endpoint	Comparison groups	NVX-CoV2373 to placebo	
	Interim analysis	VE: 1-RR Log-linear model using modified Poisson regression	89.3	

		Alpha adjusted 96.9% CI	73.0, 95.8
		P-value	< 0.0001
	Primary endpoint Final analysis	Comparison groups	NVX-CoV2373 to placebo
		VE: 1-RR Log-linear model using modified Poisson regression	89.7
		95% CI	80.2, 94.6
		P-value	< 0.001
	Key Secondary endpoint	Comparison groups	NVX-CoV2373 to placebo
		VE: 1-RR Log-linear model using modified Poisson regression	86.9
		95% CI	73.7, 93.5
		P-value	N/A

2.6.5.3. Supportive study

Study 2019nCoV-501 is an ongoing phase 2 randomised, observer blinded placebo-controlled study to evaluate the efficacy, immunogenicity and safety of NVX-CoV2373 in South African adult subjects living without HIV and safety and immunogenicity in adults living with HIV.

The primary objective of the study was to evaluate the efficacy of NVX-CoV2373 compared to placebo on the occurrence of symptomatic mild, moderate, or severe confirmed COVID-19 as demonstrated by qualitative PCR in serologically naïve (to SARS- CoV-2) healthy HIV-negative and medically stable HIV-positive adult participants (analysed as an overall population).

Methods

Eligible HIV-negative participants (Cohort 1) were healthy males/females ≥ 18 to < 85 years of age, with a BMI between 17-40 kg/m2 and a documented HIV-negative test result. Eligible HIV-positive participants (Cohort 2) were medically stable (free of opportunistic infections) males/females, ≥ 18 to < 65 years of age, with a BMI between 17-40 kg/m2, receiving highly active antiretroviral therapy using the same regimen within at least 8 weeks before screening, and having an HIV-1 viral load < 1000 copies/mL within 45 days of randomisation. Excluded participants, regardless of HIV status, included pregnant women, and persons with potential COVID-19. A negative SARS-CoV-2 results within 5 days prior to first vaccination was required. Enrolment was staggered to ensure safety. Participants 65 to < 85 years of age were only enrolled at second stage.

Participants were randomised 1:1 to receive up to 2 IM injections (Day 0 and Day 21) of SARS-CoV-2 rS with Matrix-M1 adjuvant or placebo. At 6 months (± 15 days) after the last vaccination in the initial vaccination period (Day 201), 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 CI of > 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. Secondary endpoints included the efficacy in HIV-positive and HIV-negative participants analysed separately, as well as protection against symptomatic mild or moderate or symptomatic moderate or severe COVID-19. Protection against COVID-19 requiring hospitalisation (regardless of severity) or resulting in death was also analysed.

Of note, the immunogenicity and safety objectives and endpoints are discussed in the corresponding sections of this AR.

Results

Study 2019nCoV-501 was initiated on 17 August 2020 (first participant screened) and completed enrolment into the initial phase on 25 November 2020. Participants were enrolled at 16 sites in South Africa.

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. The PP-EFF Analysis Set included 2,770 (62.7%) participants. The most frequent 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%).

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. 5.5%. were HIV-positive. 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).

Primary Efficacy Endpoint

A total of 44 cases of symptomatic mild, moderate, or severe COVID-19 cases in serologically naïve healthy HIV-negative and medically stable HIV-positive adult participants were accrued between 23 November and 30 December 2020 for the official event-driven analysis of the primary efficacy endpoint (data extraction 18 January 2021), with 15 (1.11%) cases in the NVX-CoV2373 group and 29 (2.19%) cases in the placebo group. The VE was 49.4% (95% CI: 6.1, 72.8). All but 1 case was mild or moderate in severity, with the severe case occurring in the placebo group.

Final analysis

A total of 147 symptomatic mild, moderate, or severe COVID-19 cases among all adult participants, seronegative (to SARS-CoV-2) at baseline, were accrued for the complete analysis (PP-EFF Analysis Set) of the primary efficacy endpoint (data extraction 23 February 2021), with 51 (3.62%) cases for NVX-CoV2373 versus 96 (7.05%) cases for placebo. The resultant VE of NVX-CoV2373 in prevention of symptomatic mild, moderate, or severe COVID-19 in adult participants, seronegative (to SARS-CoV-2) at baseline, was 48.6% (95% CI: 28.4, 63.1). The cumulative incidence curves in both vaccine groups is presented in Figure 11.

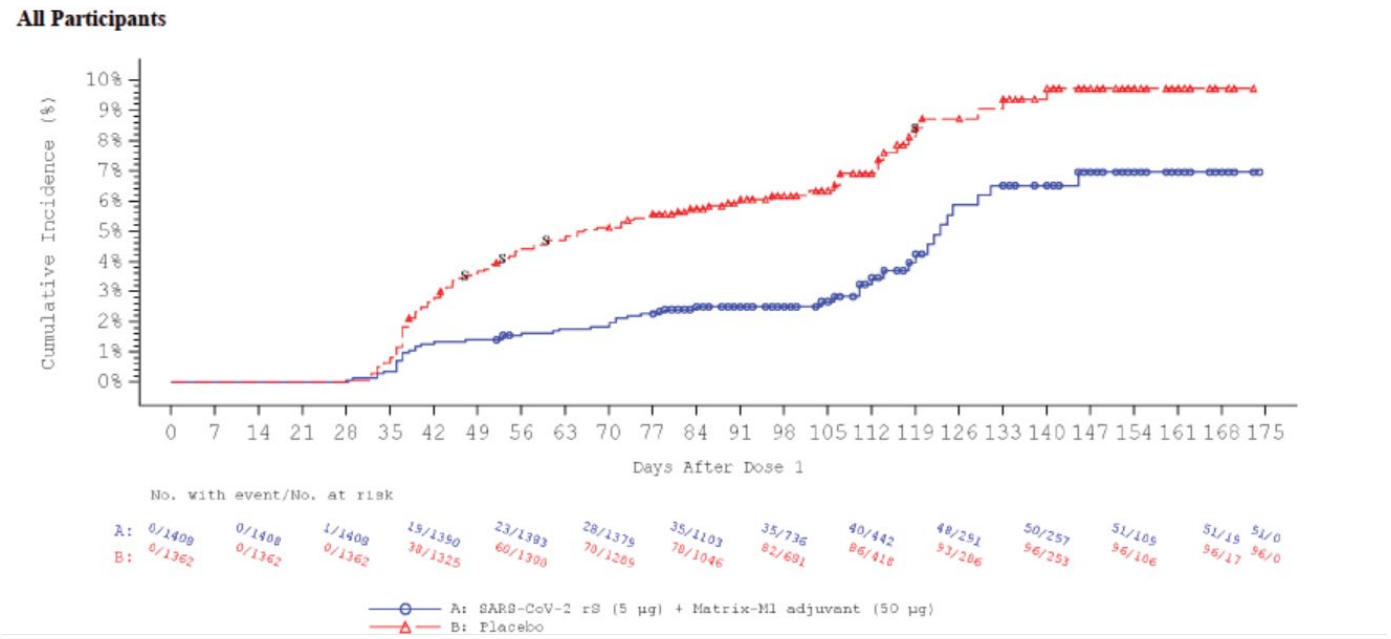


Figure 8 . Cumulative Incidence Curves for the First PCR-confirmed SARS-CoV-2 Positivity with Symptomatic Mild, Moderate or Severe COVID-19 from 7 Days after Second Vaccination (e.g., Day 28) Analysed Overall and in Serologically Naïve Healthy HIV-Negative and Medically Stable HIV-Positive Participants (PP-EFF Analysis Set, 2019nCoV-501)

Prevention of COVID-19 hospitalisation

There were 5 cases of hospitalisation among all adult participants seronegative (to SARS-CoV-2) at baseline, from 7 days after second vaccination (Day 28). All occurred in the placebo group.

Prevention of COVID-19 stratified by severity

Among all participants seronegative (to SARS-CoV-2) at baseline, from 7 days after second vaccination, the level of prevention of mild COVID-19 was 68.7%, 95% CI: 38.5, 84.1, that of moderate COVID-19 was 32.1%, 95% CI: -1.0, 54.4, and 100%, 95% CI: -5.6, 100 against severe COVID-19.

Efficacy by SARS-CoV-2 variant

Forty-one (93.2%) of 44 participants with a primary efficacy endpoint had whole genome sequence data available (samples from 3 cases in the placebo group could not be sequenced), and 38 (92.7%) of 41 were identified as the B.1.351 variant, resulting in a post-hoc VE of NVX-CoV2373 (PP-EFF Analysis Set) in prevention of symptomatic mild, moderate, or severe COVID-19 in all adult participants, seronegative (to SARS-CoV-2) at baseline, of 43.0% (95% CI: -9.8, 70.4) for the B.1.351 South African variant.

Efficacy in subgroups

By SARS-CoV-2 serostatus at baseline

A total of 147 and 39 symptomatic mild, moderate, or severe COVID-19 cases occurring at least 7 days post dose 2, among all adult participants, seronegative (to SARS-CoV-2) or seropositive at baseline were accrued for analysis. The VEs of NVX-CoV2373 in prevention of COVID-19 in all adult participants, seronegative (to SARS-CoV-2) or seropositive at baseline, were respectively 48.6% (95% CI: 28.4, 63.1) and 54.5% (95% CI: 11.1, 76.7), as shown in Table 32.

By HIV status

Among HIV-negative participants seronegative (to SARS-CoV-2) at baseline, the VE of NVX-CoV2373 in prevention of symptomatic mild, moderate, or severe COVID-19 was 55.4% (95% CI: 35.9, 68.9). Among HIV-positive participants seronegative (to SARS-CoV-2) at baseline the VE was -35.4% (95% CI: -236.9, 45.6), as shown in Table 32.

Table 25 Vaccine Efficacy of PCR-Confirmed SARS-CoV-2 Positivity with Symptomatic Mild, Moderate, or Severe COVID-19 from 7 Days after Second Vaccination (e.g., Day 28) with NVX-CoV2373 or Placebo 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, 2019nCoV-501)

Population/Baseline anti-spike IgG serostatus	No. of Cases	NVX-CoV2373		Placebo		VE (95% CI)
		n/N (%)[1]	(95% CI)	n/N (%)[1]	(95% CI)	
All participants						
Baseline seronegative[2,3]	147	51/1408 (3.62)	2.7, 4.7	96/1362 (7.05)	5.7, 8.5	48.6% (28.4, 63.1)
Baseline seropositive[4]	39	12/531 (2.26)	1.2, 3.9	27/544 (4.96)	3.3, 7.1	54.5% (11.1, 76.7)
Regardless of baseline serostatus[4]	186	63/1939 (3.25)	2.5, 4.1	123/1906 (6.45)	5.4, 7.6	49.7% (32.2, 62.6)
HIV-negative participants						
Baseline seronegative[3]	130	41/1331 (3.08)	2.2, 4.2	89/1289 (6.91)	5.6, 8.4	55.4% (35.9, 68.9)
Baseline seropositive[4]	38	12 (2.42)	1.2, 4.2	26/514 (5.06)	3.3, 7.3	52.3% (6.5, 75.6)
Regardless of baseline serostatus	168	53/1828 (2.90)	2.2, 3.8	115/1803 (6.38)	5.3, 7.6	54.5% (37.5, 67.0)
HIV-positive participants						
Baseline seronegative[3]	17	10/77 (13.0)	6.4, 22.6	7/73 (9.59)	3.94, 18.76	-35.4% (-236.9, 45.6)
Baseline seropositive[4]	1	0/34	0.0, 10.3	1/30 (3.33)	0.1, 17.2	n/a (n/a, n/a)
Regardless of baseline serostatus[4]	18	10/111 (9.01)	4.4, 15.9	8/103 (7.77)	3.4, 14.7	-16.0% (-182.5, 52.4)

2.6.6. Discussion on clinical efficacy

COVID-19 vaccine NVX-CoV2373 is meant for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. The following clinical studies were conducted by the applicant: two pivotal phase 3 trials, 2019nCoV-301 and 2019nCoV-302, and a supportive phase 2 trial, 2019nCoV-501, conducted in South Africa in approximately 4500 subjects including HIV+ subjects in addition to a phase 1/2 dose finding trial, 2019nCoV-101.

Design and conduct of clinical studies

The efficacy of the selected dose of 5 µg SARS-CoV-2 rS vaccine +50 µg Matrix-M1 adjuvant (NVX-COV2373) was assessed in two pivotal phase 3 clinical trials, 2019nCoV-302 and 2019nCoV-301. These were two randomised, observer blinded placebo-controlled trials conducted in approximately 30,000 adults aged 18 years or older in the US and Mexico (2019nCoV-301) and 15,000 adults aged 18-84 years in the UK (2019nCoV-302). The main efficacy objective of both trials was to demonstrate protective efficacy of NVX-CoV2373 given as a 2-dose vaccination regimen three weeks apart, in the prevention of virologically confirmed (by PCR to SARS-CoV-2), symptomatic coronavirus disease 2019 (COVID-19) with onset 7 days after second vaccination, as compared to placebo, in serologically negative (to SARS-CoV-2) adults.

Both studies were placebo controlled, which is acceptable as there was no authorised COVID-19 vaccine at the start of either study. In study 2019nCoV-302, single dose vials manufactured from Emergent BioSolutions (Emergent) were administered to the NVX-CoV2373 group. In study 2019nCoV-301, material filled in multi-dose vials (MDV), manufactured by Par Pharmaceutical was used.

The study population comprised of subjects 18 years and older, including individuals with underlying but stable chronic disease (e.g. diabetes, chronic lung disease, obesity) and older adults over 65 years

of age. In both studies efforts were made to include persons who were at high risk of COVID-19, aiming to include at least 25% of participants who were ≥ 65 years of age as well as prioritising other groups that are most affected by COVID-19, including racial and ethnic minorities. Pregnant and breastfeeding women were excluded from the trials as well as persons who were immune suppressed or had an immunodeficiency; few HIV+ were enrolled in supportive trial 2019nCoV-501. As both groups are highly relevant target groups for COVID-19 vaccination, it is important that the performance of NVX-CoV2373 is evaluated in these subgroups as soon as possible. Regarding children and adolescents, a paediatric development plan has been agreed with Paediatric Committee (PDCO).

In 2019nCoV-302, participants were randomised in a 1:1 ratio stratified by site and by age (18 to 64, ≥ 65 years). In 2019nCoV-301, participants were randomised in a 2:1 ratio to NVX-CoV2373 or placebo and stratified by age (18 to 64 years and ≥ 65 years). By providing full blocks to a site, the randomisation was also stratified by site. An adapted randomisation list, including randomisation time, will be shared by the applicant post-authorisation. Further, both trials were designed as single-blinded trials, with vaccination administrators potentially being aware of treatment allocation. In addition, although separate blinded and unblinded teams were set-up, any communication between the blinded and unblinded teams cannot be fully excluded and therefore blinding cannot be fully guaranteed.

The primary endpoint for both trials, i.e. the first episode of PCR-positive mild, moderate, or severe COVID-19 with onset at least 7 days after second study vaccination (Day 28), is in line with applicable regulatory guidance on the evaluation of COVID-19 vaccines, is clinically relevant and agreed. Cases were either classified as being mild, moderate or severe according to pre-defined definitions which differed slightly between the two trials. Whilst it may be argued that cases classified as moderate according to these definitions were in fact mild, this has little impact on the actual outcome of the trials as all cases regardless of severity are considered for the primary endpoint. However, it should be kept in mind for the interpretation of secondary analyses. The classification of cases was performed with a programmatic algorithm. In 2019nCoV-301, because of the potential for the programmatic algorithm to over-estimate the severity of disease (largely due to spuriously low oxygen saturations reported by participants), further medical review of all cases categorised as "severe" was performed by independent infectious disease and critical care physicians. This was not done for 2019nCoV-302. Further, the accuracy of the programmatic algorithms to distinguish mild from moderate cases is unknown, therefore categorisation of cases according to severity were not included in the SmPC. Severe cases may be reflected following review of narratives.

In general methods for case detection appear sufficiently appropriate. Assessment of probable COVID-19 cases followed reporting by study participants of respiratory and clinical signs/symptoms recognised to be predictive of COVID-19 (predefined) and subsequent laboratory confirmation of infection of SARS-CoV-2 in nasal swabs by RT-PCR. Swabs were collected through self-swabbing by individuals (2019nCoV-301, 2019nCoV-302) and by study personnel at a triggered surveillance visit (2019nCoV-301 only). Non-study swabs were permitted in 2019nCoV-302, and if a valid report existed for testing outside the study these swabs were treated identically to a study swab. Even though non-study swabs were discouraged, non-study swabs accounted for 15% of positive swabs overall. This is considerable. Furthermore, in comparison with study swabs there was a higher positivity rate in both the NVX-CoV2373 as the placebo group. The difference in positivity rate between non-study and study swabs was higher in the vaccine vs the placebo group. It is considered that this will not impact the overall conclusion of the trial. However, the applicant is expected to submit sensitivity analyses in which non-study swabs were excluded at the time of the next interim CSR submission (Q1 2022). Also, a discussion of reasons for this discrepancy in positivity rates will be expected to be submitted with these sensitivity analyses post-authorisation.

Numerous secondary endpoints were listed for both trials with varying relevance. For both trials the applicant listed 'key' secondary endpoints: protection against moderate or severe PCR confirmed

COVID-19 (2019nCoV-302) (not multiplicity controlled) and protection against COVID-19 not caused by Variants of Interest or Concern (VOI/VOC) (multiplicity controlled). Whilst protection against severe COVID-19 (including hospital admissions, ICU admissions and death) is considered an important endpoint, protection against 'moderate to severe' is considered of less relevance, particularly as the definition of moderate has large overlap with mild symptomatic disease and there is uncertainty around the accuracy of the assessment of moderate cases. Further, whilst it is considered relevant to determine whether the immune response elicited by the vaccine also protects against circulating variants which are of interest from a public health perspective due to higher transmissibility or more severe disease, this is difficult to determine, as comparisons may be biased due to the non-random introduction of these variants. It is not considered very relevant to have an estimate of efficacy against variants that are not classified as being of concern or interest, which is the key secondary endpoint for 2019nCoV-301, therefore the hierarchical testing approach is considered of limited value.

For study 2019nCoV-302 a single interim analysis of efficacy using the Lan-DeMets alpha-spending function for Pocock boundary conditions was planned to be conducted based on the accumulation of approximately 50 events of the total anticipated target number of 100 for the primary endpoint.
For study 2019nCoV-301 two interim analyses for efficacy and futility were planned targeting a total of 144 cases. However, with the implementation of the blinded crossover, the placebo-controlled portion ended, and both interim analyses were removed in a protocol revision. The DSMB was unblinded and reviewed the distribution of PCR+ cases over the trial arms during the study. The requested DSMB minutes have been provided. They provide sufficient reassurance that the timing of the interim analyses were not informed by knowledge on the efficacy of the vaccine by the DSMB. The amendment was made prior to the DSMB discussion and was therefore independently taken.

In 2019nCoV-302, the primary and secondary efficacy analyses was based on the PP-EFF and supported by ITT Analysis Sets whilst in 2019nCoV-301 the primary analysis was conducted in the PP-EFF set supported by the FAS set. Further, the primary efficacy endpoint in 2019nCoV-301 was evaluated among the seropositive and seronegative participants in the PP-EFF2 set.

The primary endpoint was analysed using modified Poisson regression, with a sensitivity analysis using a Cox proportional hazards model accounting for stratification factors. The primary hypothesis in both trials was to determine that the (multiplicity adjusted) lower bound of the confidence interval around the estimate of vaccine efficacy (100 x (1 – RR)) was above 30%. Presented statistical methods are generally considered acceptable. In study 2019nCOV-302 various strategies are applied on handling intercurrent events for each of the two proposed estimands, no estimand has been defined in study 2019nCoV-301. In addition, conventional terminology including per protocol analysis has also been used. The applicant clarified that as at the time of writing the protocol the estimand framework had not been fully implemented by all regulators globally, and it was later decided to introduce the estimand framework in the SAP. The applicant will provide supportive analysis in Q2 2022.

Sensitivity analyses assessing the impact of potential informative censoring due to early unblinding for intention to receive an Emergency Use Authorization vaccine were planned. The efficacy of NVX-CoV2373 was planned to be explored in several subgroups, such as age, presence of underlying risk factors, ethnicity and race.

In conclusion, overall, the design and conduct of the studies were appropriate and in line with the requirements as laid down in the Guideline on clinical evaluation of new Vaccines (EMA/CHMP/VWP/164653/2005) and the EMA considerations on COVID-19 vaccines approval. Overall primary and secondary efficacy objectives as defined in the phase 3 trials are of relevance to inform the efficacy of NVX-CoV2373.

Baseline data

The disposition of study participants in the various analysis sets were generally well balanced across treatment groups. A reasonable proportion of participants was over 65 years of age (27%) in 2019nCoV-302, compared to 12.6% of the safety population of 2019nCoV-301. Study 2019nCoV-301 included participants up to 95 years of age whilst -302 capped inclusion at 85 years.

Efficacy data and additional analyses

Vaccine efficacy according to the primary efficacy endpoint was demonstrated for both pivotal trials.

The inferential analysis at the interim analysis in 2019nCoV-302 indicated a VE point estimate of 89.3% with a multiplicity adjusted 96.9% CI of 73.0% to 95.8%, meeting the prespecified study success criterion of an alpha-adjusted LBCI > 30%. This interim was based on 62 accrued cases. VE was consistent in the final efficacy analysis after accrual of 106 cases, with an estimated VE of 89.7% (95%CI: 80.2, 94.6%). The final efficacy evaluation is based on a median follow-up of 90 days, limiting VE estimates to be applicable short-term. Longer-term vaccine efficacy remains currently unknown and will be further followed post-authorisation. Of the 106 cases, 4 were classified as severe (all in the placebo group). Of these, two were hospitalised. Pre-planned analyses assessing the sensitivity to model assumptions (Cox regression), missing data (tipping point analysis) as well as supportive analyses assessing different intercurrent event handling are planned by the applicant for 2022. An analysis taking into account overrunning cases not listed on the confirmed event list for the final analysis is also expected in 2022.

A single final analysis was conducted in 2019nCoV-301, based on 77 cases with 14 in the NVX-CoV2373 group and 63 in the placebo group. The resultant estimated VE was 90.4% (95% CI: 82.9, 94.6), which is in line with the findings from 2019nCoV-302. This evaluation is based on a median follow up time of 76 days after the second dose of NVX-CoV2373. There were 4 severe cases including 3 hospitalisations due to COVID-19 among the 77 per-protocol COVID-19 cases in 2019nCoV-301 (all in the placebo group). Sensitivity analyses with Cox regression were consistent (VE: 90.4%), as well as the effect in adults regardless of serostatus at baseline. The latter is unsurprising considering the small proportion of participants who were seropositive, therefore no conclusions on efficacy in seropositive subjects can be drawn. Sensitivity analyses assessing the impact of potential informative censoring due to early unblinding for intention to receive an Emergency Use Authorization vaccine are planned for 2022.

Both trials were conducted during a time that COVID-19 vaccines became available. 2019nCoV-302 was started earlier than 2019nCoV-301, September vs December 2020 respectively, and is therefore differently impacted by this. Although there was substantial unblinding in 2019nCoV-302, with one-third of participants unblinded to study vaccine assignment during the course of the study this was balanced between the groups (33.8% in the NVX-COV2373 group vs 35.4% in the placebo group). It is likely that the duration of follow-up is shorter for selective groups who were eligible first to receive an authorised vaccine through their national vaccination campaign, e.g. elderly and health care workers. However, as vaccine efficacy was fairly consistent across different risk groups and duration of follow-up is still relatively short, major impact is unlikely. In study 2019nCoV-301 there is an obvious imbalance in unblinding between the study arms, with more participants in the placebo group requesting unblinding (15.2% vs 23.4%). Overall, the percentage of unblinding is lower than in study 2019nCoV-302, however, the implementation of the blinded crossover, offering NVX-COV2373 to all participants was much earlier in the conduct of the 2019nCoV -301 study (4 months after study start) than it was in the -302 study (6 months after study start). Further, a larger proportion of participants (3.2%) did not receive their second dose in the 2019nCoV-301 trial compared to 2019nCoV-302 (1.0%), with again more participants in the placebo group (3.2% vs 4.4%). Also, a larger proportion of participants in the placebo group discontinued the study (8.1% vs 13.9%).

A trend for increased requests for unblinding to treatment received in the placebo arm compared to the NVX-COV2373 arm was observed for most clinical sites in study 2019nCoV-301, but not in study 2019nCoV-302. No obvious association between reactogenicity profile and request for unblinding has been observed, although this does not preclude that placebo recipients might still have been able to guess their treatment allocation, with potential impact on their behaviour (potentially impacting the risk of being exposed and reporting of symptoms and collection of endpoint data). To assess whether potential unblinding had an impact on the reporting of symptoms and collection of endpoint data, the applicant was requested to provide per treatment arm an overview of the unscheduled surveillance visits, number of swabs taken, number of positive and negative tested cases. There were no major differences in acute illness visits in the active and placebo arm (8.3% vs 8.7% in 2019nCOV-301and 28% vs 28% in 2019nCOV-302). The percentage of participants randomised who were tested and had a negative test result was comparable for the active and placebo arm (6.8% vs 6.6% in 2019nCOV-301 and 5.0% and 4.7% in 2019nCOV-302), while as expected a difference was observed in the percentage of positive tests. This indicates that even though in study 301 there was some awareness of the treatment received, there were likely no major differences in risks of being exposed, reporting illness or tests taken over the study arms. It is unlikely that this severely biased the efficacy estimates.

Sensitivity analyses assessing the impact of potential informative censoring due to early unblinding for intention to receive an Emergency Use Authorization vaccine were planned but have not been provided yet. Given that the lower bound of the confidence interval was far from the pre-specified null hypothesis, and based on the information provided, it is unlikely that it would change the conclusions. Sensitivity analysis are expected to be provided in Q2 2022. For both trials, cumulative incidence rates were increasing constantly after randomisation in the placebo group but remained low in the vaccine group. These analyses show that the cases in the two groups start diverging around day 21, indicating no measurable efficacy before the administration of the second dose in both trials which is further supported by analyses considering the protection after a first dose. Within the trials the vaccine was mostly given with a 3-week interval. In those who received a second dose, the at least 50% received the vaccine between day 21 and 23. Therefore it is deemed appropriate that section 4.2 of the SmPC simply states that the 2 doses are recommended to be given with a 21-day interval.

The vaccine was administered in the PP-EFF as early as day 14 up to day 60 in study 2019nCoV-301 and between day 16 and day 45 in study 2019nCoV-302, the IQR was 21 to 23 days for the ITT/FAS population in both trials. This information is reflected in section 5.1 of the SmPC.

There were insufficient severe cases (n=8) and hospitalised cases (n=5) or deaths (n=0) to reliably estimate the VE against more severe outcomes.

In 2019nCoV-301, viral genetic sequences were available for 54 of 77 primary endpoint cases in the PP-EFF. Of these, 44 cases had mutations that would identify them as a VOC or VOI, 6 in the NVX-CoV2373 group and 38 in the placebo group, suggesting that efficacy is maintained against circulating variants which included B.1.1.7 (Alpha), B.1.429 (Epsilon) and B.1.526 (Iota). There were no cases due to the B.1.617.2 (delta) variant in either trial. In 2019nCoV-302, for the final analysis, 66 cases were characterised as B.1.1.7, and 29 as Wuhan, characterisation of 11 cases is unknown. Overall, efficacy was shown against the B.1.1.7 variant. Strain specific efficacy results should however be interpreted with caution given the low number of cases for individual strains (1 vs 28 for the Wuhan strain), and potential confounding due to differences in baseline characteristics or unknown confounding factors.

In addition, subgroup analyses showed that vaccine efficacy is consistent across different risk groups, subjects with various underlying diseases and different demographic characteristics, although limited numbers in certain subgroups preclude strong conclusions.

Further support for the efficacy of NVX-CoV2373 comes from trial 2019nCoV-501 which was conducted in South Africa and included both HIV-negative and HIV-positive participants.

A total of 44 cases of symptomatic mild, moderate, or severe COVID-19 cases in serologically naïve healthy HIV-negative and medically stable HIV-positive adult participants were accrued between 23 November and 30 December 2020 for the official event-driven analysis of the primary efficacy endpoint (data extraction 18 January 2021), with 15 (1.11%) cases in the NVX-CoV2373 group and 29 (2.19%) cases in the placebo group. The estimated VE was 49.4% (95% CI: 6.1, 72.8). This is mainly driven by efficacy in HIV-negative participants, as efficacy in HIV-positive participants could not be established (overall VE -16.0%, 95% CI -182.5, 52.4). The complete analysis comprised of 147 cases, with 51 (3.6%) cases for NVX-CoV2373 versus 96 (7.1%) cases for placebo. The estimated VE was 48.6% (95% CI: 28.4, 63.1). With only few cases accrued in HIV-positive participants (10 in NVX-CoV2373 vs 8 in placebo), further evaluation of NVX-CoV2373 in HIV-positive persons would be relevant. The overall VE in this study is lower than what is observed in study 2019nCoV-302 and -301, also when looking only at the HIV-negative population. Whilst this may be explained by the circulating variant (Beta), immunogenicity results of the participants enrolled in this study also point to a reduced immune response after vaccination (measured against the Wuhan strain) compared to the response observed in 2019nCoV-302. As it is difficult to disentangle the relative contribution of the differences between the trials, it cannot be excluded that the lower VE is explained by more factors than the circulating virus variant alone, for example differences in baseline characteristics of the population enrolled or potential batch related issues.

2.6.7. Conclusions on the clinical efficacy

Based on the data available for NVX-CoV2373, a robust and high protective efficacy against COVID-19 has been demonstrated in individuals aged 18 years and older in two pivotal observer blinded placebo controlled trials. Efficacy has been established for a median follow-up of 90 days in 2019nCoV-302 and 76 days in 2019nCoV-302. 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. Lower vaccine efficacy was observed in a supportive trial 2019nCoV-501 in South Africa, which was possibly due to reduced efficacy against the Beta variant, however other factors cannot be excluded.

No major objections regarding clinical efficacy have been identified.

2.6.8. Clinical safety

Clinical safety was evaluated in the phase 1/2 trial 2019nCoV-101, phase 2 trial 2019nCoV-501 and the two pivotal phase 3 trials 2019nCoV-302 and 2019nCoV-301.

Safety assessments include monitoring and recording of solicited (local and systemic reactogenicity events), unsolicited adverse events (AEs), serious adverse events (SAEs), adverse events of special interest (AESI), and vital sign measurements. Safety laboratory values (haematology and serum chemistry) were also evaluated in the first-in-human Clinical Study 2019nCoV-101 (Part 1).

Solicited local and systemic adverse events were collected for 7 days after each vaccine dose. Grading of solicited adverse events was based on FDA Toxicity Grading Scale for Clinical Abnormalities. Unsolicited AEs were recorded from the time of first study vaccination until Day 49 after the initial set of vaccinations (i.e. 28 days post dose 2) in each trial, and for the entire study period in 2019nCoV-301. SAEs, medical attended adverse events (MAAEs) and AESIs were assessed for the entire study period in all trials.

AESIs included Potential Immune-Mediated Medical Conditions (PIMMCs) as well as events relevant to COVID-19.

The investigator was to assess causality for all AEs and SAEs. AEs will be considered related if there is a reasonable possibility of relationship to study vaccine. The AE follows a reasonable temporal sequence from administration of study vaccine and cannot be reasonably explained by the participant's clinical state or other factors (e.g., disease under study, concurrent diseases, or concomitant medications), represents a known reaction to study vaccine or other vaccines in its class, is consistent with the known pharmacological properties of the study vaccine, and/or resolves with discontinuation of the study vaccine (and/or recurs with re-challenge, if applicable).

The main presentations of data are based on the Safety Analysis sets from submitted clinical trials, including all subject data with supporting presentations to exclude the data post-unblinding/post-approved or deployed SARS-CoV-2 vaccine receipt.

For 2019nCoV-301, incidence rates for AEs were presented to account for the imbalanced randomisation and imbalanced follow up time between treatment arms. For other trials, numbers of events and % are reported.

2.6.8.1. Patient exposure

Participants from two phase 3 studies (2019nCoV-301, 2019nCoV-302), two phase 2 studies (2019nCoV-101 part 2, 2019nCoV-501) and one phase 1 study (2019nCoV-101 part 1) contributed to the safety database for NVX-CoV2373. In total 30,058 subjects have been exposed to at least one dose of NVX-CoV2373 (5 ug rS /50 ug adjuvant), with 19,892 participants receiving a placebo. Of these, over 96% have received two doses.

Table 26. Exposure of Participants in the Pooled Analysis of Safety Data

Number of Doses Received	NVX-CoV2373	Placebo
Total exposure	30058	19892
2 doses	28963 (96.4%)	19270 (96.9%)
1 dose[1]	1095 (3.6%)	622 (3.1%)

Abbreviations: 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. Participants receiving a mixed regimen are included in the pooled analysis of safety data as receiving 1 dose of the active vaccine and only the data post the active vaccine dose are included in the analysis. They were not included in the analysis of short-term safety post the second dose of the active vaccine.

Source: T2

In the phase 1 study, 134 subjects aged 18-59 were randomised. Of these, 29 subjects received 2 doses of the final formulation (5 ug rS /50 ug adjuvant) and 54 subjects received at least 1 dose of 25 ug/50 ug vaccine formulation. In the phase 2 study 2019nCoV-101 (part 2), 1288 subjects were randomised, 1,283 participants received at least 1 dose of trial vaccine and 1,256 participants received both Dose 1 and Dose 2. Of these, 260 subjects received a single dose of NVX-CoV2373 (5 ug rS /50 ug adjuvant), 254 subjects received two doses. In addition, 251 subjects received two doses and 263 subjects received one dose of 25 ug/50 ug vaccine formulation (with a higher level of S-protein).

The exposure in other phase 2 and 3 studies in presented in the table below.

Table 27. Exposure in phase 2 and phase 3 studies evaluating NVX-CoV2373

	Target population	Participants enrolled (NVX-CoV2373 / Placebo)	Received 1st dose (NVX-CoV2373 / Placebo)	Received 2nd dose (NVX-CoV2373 / Placebo)	Follow up time* (NVX-CoV2373 / Placebo)	Date Cut Off
2019nCoV-302	18-84 yrs, incl. participants with comorbidities	7593/7594	7,569/7,570	7,467/7,463	Median: 90.0 / 90.0	23-02-2021
2019nCoV-301	18-84 yrs, incl. participants with comorbidities	19,965/9,984	19,729/9,853	19,104/9,422	Median: 76.0/77.0	01-06-2021
2019nCoV-501	18-84 yrs; healthy HIV- & medically stable adult HIV+	2,211/2,197	2,211/2,197	2,140/2,120	Median: 75.0/75.0	23-02-2021

* as presented in the interim CSRs submitted, from the second dose

The median duration of follow-up in the pooled safety database was 70 days post-Dose 2, with 32,993 (66%) participants completing more than 2 months follow-up post-Dose 2. The shorter median duration of follow-up in the pooled data as compared to the individual studies is due to censoring at unblinding.

2.6.8.2. Adverse events

Solicited local reactions

There were higher frequencies of solicited local AEs among NVX-CoV2373 recipients than among placebo recipients in all trials. An overview of solicited local AEs is presented in Table 35.

In 2019nCoV-302, following the first dose, solicited local AEs were reported by 59.3% of NVX-CoV2373 recipients compared to 20.9% of placebo recipients. Following second dose the frequency of solicited local AEs in the NVX-CoV2373 group (80.2%) increased relative to the first vaccination (59.3%) and remained higher than in the placebo group (17.0%). Also, higher frequencies of grade 3 reactions were reported following the second dose, increasing from 1.1% to 5.2%. There was a slight increase in the frequency and intensity of reactions following the second dose in persons who reported mild (grade 0, grade 1) reactions following the first dose; of persons reporting grade 1 reactions following the first dose approximately 50% reported grade 2 or higher reactions following the second dose. Persons reporting moderate to severe reactions following the first dose tended to report similar or less severe reactions following the second dose.

Tenderness and injection site pain were the most frequent solicited local AEs, reported by 705 (54.9%) and 394 (30.7%) participants, respectively, after the first dose and by 922 (76.6%) and 624 (51.9%) participants after the second dose. Median durations of tenderness and pain increased with the second dose from 2.0 to 3.0 and 1.0 to 2.0 days respectively. A similar picture emerged in 2019nCoV-301 and 2019nCoV-101. In 2019nCoV-501 lower rates of local reactions were reported following the second dose compared to the first and they were less often severe.

Table 28. 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.

Solicited systemic reactions

Overall, there were higher frequencies of solicited systemic AEs among NVX-CoV2373 recipients than among placebo recipients following each vaccination overall and in each age cohort. An overview of solicited systemic AEs after each dose across the clinical trials is presented in Table 29

Table 29. 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.

In 2019nCoV-302, solicited systemic AEs were reported by 47.6% of NVX-CoV2373 recipients following the first dose. This increased with the second dose to 64.6%. With the second dose, higher frequencies of grade 3 reactions were reported, increasing from 1.3% with the first dose to 6.8%. There was a modest increase in the frequency and intensity of reactions with the second dose for those persons who experienced mild (grade 0, grade 1) reactions with the first dose. Of participants reporting grade 1 reactions with the first dose, 55% reported grade 2 or higher reactions following the second dose. Of participants who reported grade 3 or 4 reactions following the first dose, 60% reported less severe systemic reactions following the second dose.

Headache, fatigue, and muscle pain were the most frequent solicited systemic AEs. Grade 3 headache, fatigue, and muscle pain were reported in 17 (1.4%), 43 (3.6%), and 34 (2.8%) participants in the NVX-CoV2373 group and 3 (0.3%), 9 (0.8%), and 3 (0.3%) participants in the placebo group. Median durations of headache, fatigue, and muscle pain were 1.0, 1.0, and 1.0 day in each study vaccine group after both the first as the second dose.

Again, a similar systemic reactogenicity was observed in trials 2019nCoV-101 and 2019nCoV-301. In 2019nCoV-301, 0.1% reported grade 4 solicited systemic adverse events after the first and second dose in both vaccine arms.

Following first vaccination in 2019nCoV-301, overall concomitant analgesic medication use was low (< 1%), and rates were balanced between the NVX-CoV2373 and placebo groups (130 [0.7%] and 57 [0.6%], respectively). Following second vaccination, there was an increase in concomitant analgesic medication use in the NVX-CoV2373 group relative to the placebo group (545 [2.8%] and 63 [0.6%], respectively). In 2019nCoV-302, following first vaccination, overall concomitant analgesic medication use was low (1.4%), and rates were balanced between the NVX-CoV2373 and placebo groups (100 [1.3%] and 112 [1.5%], respectively). Similar results were seen following second vaccination (103 [1.4%] and 119 [1.6%], respectively).

Unsolicited adverse events

There were higher frequencies of unsolicited AEs within the 49 days after first vaccination among NVX-CoV2373 recipients than among placebo recipients. Unsolicited AEs were mostly mild, with severe TEAEs occurring in < 1% of participants.

In **2019nCoV-301**, up to Day 49, higher rates of AEs in the NVX-CoV2373 group were reported for the following SOCs:

'General disorders and administration site conditions' (IR: 33.7 vs 16.8 per 100 PY) with differences in the PTs: Fatigue, Injection site pain, pain, pyrexia, chills, malaise, injection site pruritus, injection site erythema, Injection site swelling, influenza like illness, oedema peripheral (n=15 vs 4).

Nervous system disorders (IR: 18.7 vs 18.1 per 100 PY) with differences in PTs Headache (n=293 vs 130), Migraine (n=18 vs 3)

'Musculoskeletal and connective tissue disorders' (IR: 13.8 vs 11.8 per 100 PY), with a difference in PTs Myalgia (n=109 vs 30), Pain in extremity (n=51 vs 17), tendonitis (n=11 vs 2)

'Skin and subcutaneous tissue disorders' (IR: 7.9 vs 5.2), with a difference in the PTs Rash (n=61 vs 22), Pruritus (n=25 vs 2), Urticaria (n=17 vs 5), Erythema (n=16 vs 3).

'Blood and lymphatic disorders' (IR: 2.8 vs 1.6), with a difference in the PT Lymphadenopathy (n=53 vs 13)

'Eye disorders' (IR: 2.3 vs 1.0) with 62 events reported in 51 of 19,729 (0.26%) participants receiving active vaccine compared with 13 events in 12 of 9,853 (0.12%) placebo-treated participants. This explained by minor imbalances in several PTs including diplopia (notably, one SAE of diplopia was reported), dry eye, eye swelling, lacrimation increased, ocular discomfort, photophobia, and swelling of eyelid. Several of these PTs are related or can possibly be caused by inflammation of the eye although there was only a singular report in the PT 'Eye inflammation' (in the NVX-CoV2373 group).

Reproductive system and breast disorders (IR: 2.00 vs 1.25) with 55 events reported in 52 of 19,729 (0.26%) participants receiving active vaccine compared with 17 events in 17 of 9,853 (0.17%) placebo-treated participants; the imbalance is explained by PTs of dysmenorrhoea (12 vs 3) and menstruation irregular (5 vs 0).

There was a higher IR of unsolicited treatment-related AEs reported from start of first vaccination through 28 days after second vaccination (eg, Day 49) in the NVX-CoV2373 group (50.92 e/100 PY]) than in the placebo group (26.34 e/100 PY). Unsolicited treatment-related AEs that had a > 1.00 e/100 PY higher IR in the NVX-CoV2373 group than in the placebo group were injection site pain (5.64 vs 2.35), fatigue (4.84 vs 2.72), headache (4.73 vs 3.31), pyrexia (2.76 vs 0.74), myalgia (2.76 vs 0.96), chills (1.86 vs 0.37), and injection site pruritus (1.53 vs 0.15); these events were consistent with the solicited local and systemic TEAEs reported during the reactogenicity period.

In **2019nCoV-302**, differences between the treatment arms were largely due to differences in AEs of pain (1.2% vs 0.3%, respectively), injection site pruritus (0.7% vs <0.1%), and lethargy (1.0% vs 0.4%). There was a higher frequency of participants with unsolicited treatment-related AEs in the NVX-CoV2373 group (10.9%) than in the placebo group (4.6%); this difference was largely due to treatment-related AEs of pain (1.1% vs 0.2%, respectively), influenza-like illness (0.8% vs <0.1%), injection site pruritus (0.6% vs <0.1%), and lethargy (0.9% vs 0.3%).

Considering the severe AEs in 2019nCoV-302, a numerical imbalance was seen for hypertension, with 9 reports of hypertension (0.1%) for the NVX-CoV2373 group compared with 2 for the placebo group (<0.1%), in addition to reports of blood pressure increased (n=2), systolic hypertension (n=1) and hypertensive crisis (n=1) in the NVX-CoV2373 group vs one report of 'blood pressure systolic

increased' in the placebo group (n=1). Combined 13 vs 3 severe TEAEs were reported related to hypertension. In the *pooled analysis* the incidence rates were 0.40 (n=102) in the NVX-CoV2373 arm compared to 0.43 (n=70) in the placebo arm for participants 18-64 years. In participants aged 65 or older however, the rates were 0.96 (n=46) in the NVX-CoV2373 arm compared to 0.64 (n=22) in the placebo group during the 3 days following vaccination.

In **2019nCoV-501**, there was a similar rate of unsolicited AEs through 49 days after first vaccination in both vaccine arms. The most frequent (incidence > 1.0%) TEAEs in the NVX-CoV2373 group were headache (3.1%) and upper respiratory tract infection (1.2%); headache (2.3%) and influenza-like illness (1.1%) were the most frequent in the placebo group. The most frequent (incidence > 5 participants) treatment-related TEAEs in the NVX-CoV2373 group were headache (17 [0.8%]), myalgia (9 [0.4%]), lymphadenopathy (9 [0.4%]), and injection site pain (6 [0.3%]).

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.

PIMMCs were reported in 5 (<0.1%) participants in the NVX-CoV2373 group and 8 (0.1%) participants in the placebo group in 2019nCoV-302. There were no PIMMCs reported for 2019nCoV-501 and 2019nCoV-101.

In 2019nCoV-301 there was a higher IR of PIMMCs reported from start of first vaccination to blinded crossover or End of Study in the NVX-CoV2373 group (0.40 e/100 PY]) than in the placebo group (0.15 e/100 PY). An overview of PIMMCs reported in 2019nCoV-301 is presented in Table 37.Table 30 Apart from uveitis (n=3 reports) and Basedow's disease/hyperthyroidism (n=3), there was only a single report for the PTs listed with no clear patterns emerging aside from the overall imbalance.

Table 30 . Overall Summary of Potential Immune-Mediated Medical Conditions Based on Protocol-Defined MedDRA Preferred Terms or Site Entered Criteria on the Case Report Form

by System Organ Class and Preferred Term Reported from After Start of First Vaccination to Blinded Crossover or End of Study by Age Strata (Safety Analysis Set)

System Organ Class/ Preferred Term (MedDRA, Version 23.1)	All Participants ≥ 18 Years				Participants 18 to ≤ 64 Years				Participants ≥ 65 Years			
	NVX-CoV2373 N = 19729		Placebo N = 9853		NVX-CoV2373 N = 17251		Placebo N = 8616		NVX-CoV2373 N = 2478		Placebo N = 1237	
	E	IR	E	IR	E	IR	E	IR	E	IR	E	IR
Number of participants experiencing an event	**33**	**0.62**	**14**	**0.54**	**29**	**0.63**	**12**	**0.53**	**4**	**0.58**	**2**	**0.59**
Nervous system disorders	**13**	**0.25**	**6**	**0.23**	**12**	**0.26**	**4**	**0.18**	**1**	**0.14**	**2**	**0.59**
Seizure	4	0.08	3	0.11	4	0.09	3	0.13	0	0	0	0
Neuropathy peripheral	3	0.06	2	0.08	3	0.07	0	0	0	0	2	0.59
Central nervous system inflammation	1	0.02	0	0	1	0.02	0	0	0	0	0	0
Facial paralysis	1	0.02	0	0	1	0.02	0	0	0	0	0	0
Hypoaesthesia	1	0.02	1	0.04	1	0.02	1	0.04	0	0	0	0
Narcolepsy	1	0.02	0	0	1	0.02	0	0	0	0	0	0
Neuralgia	1	0.02	0	0	0	0	0	0	1	0.14	0	0
Peroneal nerve palsy	1	0.02	0	0	1	0.02	0	0	0	0	0	0
Skin and subcutaneous tissue disorders	**5**	**0.09**	**2**	**0.08**	**5**	**0.11**	**2**	**0.09**	**0**	**0**	**0**	**0**
Alopecia areata	2	0.04	0	0	2	0.04	0	0	0	0	0	0
Psoriasis	2	0.04	0	0	2	0.04	0	0	0	0	0	0
Erythema nodosum	1	0.02	0	0	1	0.02	0	0	0	0	0	0
Lichen planus	0	0	1	0.04	0	0	1	0.04	0	0	0	0
Lichenoid keratosis	0	0	1	0.04	0	0	1	0.04	0	0	0	0
Endocrine disorders	**4**	**0.08**	**1**	**0.04**	**3**	**0.07**	**1**	**0.04**	**1**	**0.14**	**0**	**0**
Basedow's disease	2	0.04	0	0	1	0.02	0	0	1	0.14	0	0
Autoimmune thyroiditis	1	0.02	1	0.04	1	0.02	1	0.04	0	0	0	0
Hyperthyroidism	1	0.02	0	0	1	0.02	0	0	0	0	0	0
Eye disorders	**4**	**0.08**	**1**	**0.04**	**4**	**0.09**	**1**	**0.04**	**0**	**0**	**0**	**0**
Uveitis	3	0.06	1	0.04	3	0.07	1	0.04	0	0	0	0
Iridocyclitis	1	0.02	0	0	1	0.02	0	0	0	0	0	0
Musculoskeletal and connective tissue disorders	**2**	**0.04**	**2**	**0.08**	**1**	**0.02**	**2**	**0.09**	**1**	**0.14**	**0**	**0**
Arthritis	1	0.02	0	0	1	0.02	0	0	0	0	0	0
Polymyalgia rheumatica	1	0.02	0	0	0	0	0	0	1	0.14	0	0
Rheumatoid arthritis	0	0.00	2	0.08	0	0	2	0.09	0	0	0	0
Gastrointestinal disorders	**2**	**0.04**	**1**	**0.04**	**1**	**0.02**	**1**	**0.04**	**1**	**0.14**	**0**	**0**
Colitis ulcerative	1	0.02	0	0	0	0	0	0	1	0.14	0	0
Crohn's disease	1	0.02	0	0	1	0.02	0	0	0	0	0	0
Coeliac disease	0	0.00	1	0.04	0	0	1	0.04	0	0	0	0
Blood and lymphatic system disorders	**1**	**0.02**	**1**	**0.04**	**1**	**0.02**	**1**	**0.04**	**0**	**0**	**0**	**0**
Thrombocytopenia	1	0.02	1	0.04	1	0.02	1	0.04	0	0	0	0
Infections and infestations	**1**	**0.02**	**0**	**0**	**1**	**0.02**	**0**	**0**	**0**	**0**	**0**	**0**
COVID-19	1	0.02	0	0	1	0.02	0	0	0	0	0	0
Investigations	**1**	**0.02**	**0**	**0**	**1**	**0.02**	**0**	**0**	**0**	**0**	**0**	**0**
Heparin-induced thrombocytopenia test	1	0.02	0	0	1	0.02	0	0	0	0	0	0

Abbreviations: AE = adverse event; E = number of AEs reported; IR = incidence rate is defined as number of events per 100 person-years = e/100 PY; MedDRA = Medical Dictionary for Regulatory Activities; NVX-CoV2373 = 5 µg SARS-CoV-2 rS with 50 µg Matrix-M1 adjuvant; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SARS-CoV-2 rS = severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine.
Source: T14.3.4.13.2

Given findings in the interim data outputs, which suggested that investigators (and perhaps participants) thought they could surmise the treatment assignment, a broader analysis with respect to PIMMCs was undertaken. A standard MedDRA query (SMQ) based on the protocol-defined PIMMC MedDRA preferred terms was applied to the data. This evaluation demonstrated no imbalance of PIMMCs between study groups. An overview of PIMMCs based on protocol-defined MedDRA preferred terms or site entered criteria on case report forms is provided in the table above. There were no SOCs that had a ≥ 0.05 e/100 PY higher IR in the NVX-CoV2373 group than in the placebo group.

In 2019nCoV-302 similar frequencies of participants reported protocol-defined **AESIs relevant to COVID-19** between the NVX-CoV2373 and placebo groups, with AESIs reported in 8 (0.1%) participants in the NVX-CoV2373 group and 23 (0.3%) participants in the placebo group. Anosmia and ageusia were the most frequently reported AESIs relevant to COVID-19, reported by 0.1% in the NVX-COV2373 group. In 2019nCoV-301, there was a numerically higher IR of AESIs relevant to COVID-19

reported from start of first vaccination to blinded crossover or EoS in the placebo group (0.27 e/100 PY]) than in the NVX-CoV2373 group (0.11 e/100 PY). IN 2019nCoV-501, there were few reports of AESIs related to COVID-19 through 49 days after first vaccination: 11 (0.5%) participants in the NVX-CoV2373 group and 14 (0.6%) participants in the placebo group. AESIs related to COVID-19 in the NVX-CoV2373 group were anosmia, cough, oropharyngeal pain, and pyrexia (3 [0.1%] each).

2.6.8.3. Serious adverse events and deaths

Deaths

Three (<0.1%) participants died during study 2019nCoV-302, 2 in the NVX-CoV2373 group and 1 in the placebo group. In 2019nCoV-301, a total of 14 participants died during the study, with 9 (0.05%) in the NVX-CoV2373 group and 5 (0.05%) in the placebo group. Four deaths occurred in 2019nCoV-501, with 2 deaths (unknown cause and COVID-19) in the NVX-CoV2373 group and 2 deaths (both COVID-19) in the placebo group. There were no deaths reported in 2019nCoV-101 (interim report).

All deaths were assessed as not related to trial vaccine. An overview of deaths occurring within clinical trials is provided in Table 31

Table 31 Incidence Rates of Death Events Reported from After Start of First Vaccination Through the Respective Data Cutoff Dates of the Individual Clinical Trials 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 N1 = 25282	Placebo N1 = 16433	NVX-CoV2373 N1 = 4776	Placebo N1 = 3459
Total follow-up time (person-years)	**6337.9**	**4074.4**	**1127.1**	**802.8**
Median follow-up time after first vaccination (days)	**93**	**92**	**91**	**88**
Any deaths	**7 (0.11)**	**5 (0.12)**	**5 (0.44)[1]**	**3 (0.37)**
Cardiac disorders	**2 (0.03)**	**3 (0.07)**	**1 (0.09)**	**1 (0.12)**
Cardiac arrest	2 (0.03)	3 (0.07)	1 (0.09)	0
Myocardial infarction	0	0	0	1 (0.12)
General disorders and administration site conditions	**1 (0.02)**	**0**	**1 (0.09)**	**0**
Death	0	0	1 (0.09)	0
Sudden death	1 (0.02)	0	0	0
Infections and infestations	**2 (0.03)**	**2 (0.05)**	**1 (0.09)**	**2 (0.25)**
COVID-19 pneumonia	1 (0.02)[2]	0	0	0
Septic shock	1 (0.02)	0	0	0
COVID-19	0	2 (0.05)	1 (0.09)[3]	1 (0.12)
Bacterial sepsis	0	0	0	1 (0.12)
Injury, poisoning and procedural complications	**1 (0.02)**	**0**	**1 (0.09)**	**0**
Gunshot wound	1 (0.02)	0	0	0
Poisoning deliberate	0	0	1 (0.09)	0
Nervous system disorders	**0**	**0**	**1 (0.09)**	**0**
Cerebrovascular accident	0	0	1 (0.09)	0
Vascular disorders	**1 (0.02)**	**0**	**0**	**0**
Circulatory collapse	1 (0.02)	0	0	0

Abbreviations: COVID-19 = coronavirus disease 2019; MedDRA = Medical Dictionary for Regulatory Activities; PP-EFF = Per-Protocol Efficacy; 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. This analysis censored 1 participant in the NVX-CoV2373 group who died due to myocardial infarction approximately 2 months after the participant was unblinded to treatment assignment due to receipt of an EUA vaccine (this event was included in the 2019nCoV-301 Interim Report).
2. One NVX-CoV2373 participant in Clinical Study 2019nCoV-302 died due to COVID-19 pneumonia, which was reported 12 days after the first dose of vaccine; this event was excluded from the PP-EFF analysis because the event occurred before 7 days after second vaccination.
3. One NVX-CoV2373 participant in Clinical Study 2019nCoV-501 died due to COVID-19, which was reported 1 day after the participant received the second dose of vaccine; this event was excluded from the PP-EFF analysis because the event occurred before 7 days after second vaccination.

Note: Results are presented as number of events per 100 person-years, with the event rate in parentheses.
Source: T31.1.1a, T31.1.2a

Other serious adverse events

The IRs of unsolicited SAEs reported from after the start of first vaccination through the respective data cut-off dates for each individual study with an IR > 0.10 events per 100 person-years (e/100 PY) in any study group are presented in Table 39. SAEs occurred at a similar rate across both treatment groups, with slightly higher IRs among participants in the older age cohort (≥ 65 years of age).

Table 32 . Incidence Rates of Serious Adverse Events Reported from After Start of First Vaccination Through the Respective Data Cutoff Dates of the Individual Clinical Trials with an Incidence Rate > 0.10 e/100 PY 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
Total follow-up time (person-year)	**6337.9**	**4074.4**	**1127.1**	**802.8**
Median follow-up time after first vaccination (days)	**93**	**92**	**91**	**88**
Any SAE	**208 (3.28)**	**144 (3.53)**	**76 (6.74)**	**53 (6.60)**
Infections and infestations	**35 (0.55)**	**41 (1.01)**	**11 (0.98)**	**14 (1.74)**
Appendicitis	6 (0.09)	6 (0.15)	1 (0.09)	1 (0.12)
COVID-19	4 (0.06)	9 (0.22)	4 (0.35)	2 (0.25)
Pneumonia	2 (0.03)	1 (0.02)	2 (0.18)	4 (0.50)
COVID-19 pneumonia	1 (0.02)	10 (0.25)	0 (0.00)	2 (0.25)
Cellulitis	1 (0.02)	1 (0.02)	1 (0.09)	1 (0.12)
Sepsis	1 (0.02)	1 (0.02)	1 (0.09)	1 (0.12)
Arthritis bacterial	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.12)
Bacterial sepsis	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.12)
Streptococcal bacteraemia	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.12)
Injury, poisoning and procedural complications	**28 (0.44)**	**18 (0.44)**	**12 (1.06)**	**3 (0.37)**
Fall	1 (0.02)	2 (0.05)	0 (0.00)	1 (0.12)
Femur fracture	1 (0.02)	0 (0.00)	2 (0.18)	0 (0.00)
Wrist fracture	1 (0.02)	0 (0.00)	1 (0.09)	1 (0.12)
Femoral neck fracture	0 (0.00)	1 (0.02)	0 (0.00)	1 (0.12)
Cardiac disorders	**20 (0.32)**	**12 (0.29)**	**15 (1.33)**	**7 (0.87)**
Atrial fibrillation	5 (0.08)	1 (0.02)	2 (0.18)	2 (0.25)
Acute myocardial infarction	2 (0.03)	1 (0.02)	2 (0.18)	1 (0.12)
Myocardial infarction	2 (0.03)	1 (0.02)	1 (0.09)	1 (0.12)
Acute left ventricular failure	1 (0.02)	0 (0.00)	2 (0.18)	0 (0.00)
Atrioventricular block complete	1 (0.02)	0 (0.00)	0 (0.00)	1 (0.12)
Cardiac failure congestive	1 (0.02)	1 (0.02)	2 (0.18)	0 (0.00)
Coronary artery disease	1 (0.02)	1 (0.02)	0 (0.00)	1 (0.12)
Atrial tachycardia	0 (0.00)	0 (0.00)	2 (0.18)	0 (0.00)
Arrhythmia	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.12)
Nervous system disorders	**20 (0.32)**	**13 (0.32)**	**3 (0.27)**	**1 (0.12)**
Cerebrovascular accident	5 (0.08)	0 (0.00)	2 (0.18)	1 (0.12)
Gastrointestinal disorders	**17 (0.27)**	**5 (0.12)**	**2 (0.18)**	**5 (0.62)**
Intestinal perforation	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.12)
Nausea	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.12)
Obstructive pancreatitis	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.12)
Small intestinal obstruction	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.12)
Vomiting	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.12)
Hepatobiliary disorders	**12 (0.19)**	**0 (0.00)**	**0 (0.00)**	**1 (0.12)**
Liver injury	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.12)
Psychiatric disorders	**12 (0.19)**	**8 (0.20)**	**0 (0.00)**	**2 (0.25)**
Suicidal ideation	3 (0.05)	2 (0.05)	0 (0.00)	1 (0.12)
Bipolar disorder	2 (0.03)	0 (0.00)	0 (0.00)	1 (0.12)
Respiratory, thoracic and mediastinal disorders	**12 (0.19)**	**7 (0.17)**	**5 (0.44)**	**4 (0.50)**
Dyspnoea	2 (0.03)	1 (0.02)	0 (0.00)	1 (0.12)
Pulmonary embolism	2 (0.03)	2 (0.05)	2 (0.18)	1 (0.12)
Acute respiratory failure	1 (0.02)	0 (0.00)	2 (0.18)	0 (0.00)
Asthma	1 (0.02)	1 (0.02)	0 (0.00)	1 (0.12)
Epistaxis	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.12)

Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**11 (0.17)**	**6 (0.15)**	**8 (0.71)**	**5 (0.62)**
Prostate cancer	2 (0.03)	0 (0.00)	3 (0.27)	0 (0.00)
Non-Hodgkin's lymphoma	0 (0.00)	0 (0.00)	1 (0.09)	1 (0.12)
Adenocarcinoma of appendix	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.12)
Glioblastoma	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.12)
Ovarian cancer	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.12)
Squamous cell carcinoma of the tongue	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.12)
Vascular disorders	**8 (0.13)**	**5 (0.12)**	**4 (0.35)**	**1 (0.12)**
Deep vein thrombosis	0 (0.00)	0 (0.00)	2 (0.18)	0 (0.00)
Peripheral ischaemia	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.12)
Blood and lymphatic system disorders	**5 (0.08)**	**2 (0.05)**	**0 (0.00)**	**2 (0.25)**
Anaemia	1 (0.02)	0 (0.00)	0 (0.00)	1 (0.12)
Iron deficiency anaemia	1 (0.02)	0 (0.00)	0 (0.00)	1 (0.12)
General disorders and administration site conditions	**3 (0.05)**	**4 (0.10)**	**5 (0.44)**	**2 (0.25),**
Chest pain	1 (0.02)	2 (0.05)	0 (0.00)	1 (0.12)
Asthenia	0 (0.00)	0 (0.00)	2 (0.18)	0 (0.00)
Oedema	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.12)
Metabolism and nutrition disorders	**3 (0.05)**	**8 (0.20)**	**1 (0.09)**	**1 (0.12)**
Hypoalbuminaemia	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.12)
Musculoskeletal and connective tissue disorders	**3 (0.05)**	**3 (0.07)**	**3 (0.27)**	**0 (0.00)**
Renal and urinary disorders	**2 (0.03)**	**6 (0.15)**	**4 (0.35)**	**2 (0.25)**
Acute kidney injury	1 (0.02)	1 (0.02)	2 (0.18)	1 (0.12)
Renal failure	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.12)
Reproductive system and breast disorders	**2 (0.03)**	**0 (0.00)**	**1 (0.09)**	**1 (0.12)**
Benign prostatic hyperplasia	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.12)
Surgical and medical procedures	**2 (0.03)**	**1 (0.02)**	**0 (0.00)**	**1 (0.12)**
Spinal fusion surgery	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.12)
Investigations	**0 (0.00)**	**2 (0.05)**	**0 (0.00)**	**1 (0.12)**
Blood pressure systolic increased	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.12)

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 in the older age cohort 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.
Source: T28.1.1, T28.1.2

In **2019nCoV-301** 169 (0.86%) participants in the NVX-CoV2373 group reported 228 SAEs (IR: 4.32/100PY). There were 128 SAE reported in the placebo group (IR: 4.89/100PY).

Two SAEs (angioedema and central nervous system inflammation) in the NVX-CoV2373 group were assessed by both the investigator and sponsor as being related to study vaccine. Three additional SAEs (Basedow's disease, hyperthyroidism, and thrombocytopenia) in the NVX-CoV2373 group were assessed by the investigator as related to study vaccine but were assessed by the sponsor as not related to study vaccine. Also refer to AESIs.

Other SAEs of interest in 2019nCoV-301 due to imbalances between the treatment arms or observations in other trials are:

- There were 11 events of (acute) cholecystitis, bile duct stone, and cholelithiasis reported in nine subjects in the NVX-CoV2373 group and none in the placebo group
- There were 6 events of prostate cancer in the NVX-CoV2373 group and none in the placebo group. These events occurred in 5 subjects
- There were 7 events of cerebrovascular accident in the NVX-CoV2373 group and one in the placebo group. These events occurred in 8 subjects, including one in the placebo group

There were 4 events of hypertension and 2 events of hypertensive crisis reported as an SAE in the NVX-CoV2373 group, and none in the placebo group.

In **2019nCoV-302,** 44 (0.6%) participants in the NVX-CoV2373 group reported 54 SAEs vs 44 (0.6%) participants in the placebo group reporting 56 SAEs. One SAE of myocarditis in a 18-29 year old study participant with no underlying risk factors was considered related to study vaccine by the investigator; TTO was 3 days post second vaccination. The event resolved. Further, there was an SAE of pulmonary embolism in a 50-59 year old study participant with relevant risk factors. TTO was 9 days after the second vaccination. The event was not considered related to vaccination by the investigator.

In **2019nCoV-501**, a total of 11 (0.5%) participants reported 11 SAEs in the NVX-CoV2373 group and 18 (0.8%) participants reported 18 SAEs in the placebo group; none of these events in either group were assessed as related to trial vaccine.

There were no SAEs reported in **2019nCoV-101** (Part 1) (D189 interim report). In study 2019nCoV-101 (Part 2) 9 (0.7%) participants had a total of 9 SAEs, including an SAE of colitis occurring 2 days post second dose and assessed as not related by the Sponsor.

2.6.8.4. Laboratory findings

Clinical laboratory findings were only reported for study 2019nCoV-101 (Part 1), where haematology and serum chemistry was part of the safety assessments. Haemoglobin, haematocrit, platelet count, white blood cell count, alanine aminotransferase, aspartate aminotransferase, bilirubin, creatine were determined. FDA toxicity grading was applied.

Haematology: A total of 6 participants (4.6%) had post-baseline Grade ≥ 2 hematologic laboratory abnormalities: 1 in Group A [placebo/placebo], 1 in Group B [25/0 µg × 2], 2 in Group C [5/50 µg × 2], and 2 in Group E [25/50 µg, Dose 1; placebo, Dose 2]. This included 5 participants (3.8%) with Grade 3 toxicity (1 in Group B; 2 in Group C; and 2 in Group E). All Grade ≥ 2 hematologic laboratory abnormalities comprised decreased haemoglobin, defined as > 20 g/L decreases from baseline. These events were predominantly transient in nature. Median haemoglobin values decreased from baseline across the active vaccine and placebo groups following first vaccination at Day 7 and at Day 21 and following second vaccination at Day 28.

Serum chemistry: A total of 2 participants (1.5%) had abnormal serum chemistry laboratory values reported as TEAEs (liver function test increased in Group C and transaminases increased in Group D). Both events were mild in severity and assessed as related to active vaccine.

A total of 10 participants (7.6%) had post-baseline Grade ≥ 2 serum chemistry abnormalities (1 in Group A [placebo/placebo], 1 in Group B [25/0 µg × 2], 2 in Group C, 5 in Group D, and 1 in Group E [25/50 µg, Dose 1; placebo, Dose 2]), which included 2 participants (1.5%) with Grade 3 toxicity (1 each in Groups C and E); no participant had a Grade 4 serum chemistry abnormality.

Throughout the clinical trials, there were similar rates of laboratory investigation TEAEs for NVX-CoV2373 compared with placebo. TEAEs in most PTs were infrequent, with less than two events for most PTs in either the NVX-CoV2373 or placebo groups; there were no clear imbalances between the NVX-CoV2373 group and placebo.

2.6.8.5. Safety in special populations

By sex

In the pivotal trial 2019nCoV-302, 51.6% of participants were male and 48.4% were female. In the pivotal trial 2019nCoV-301, 52.2% of participants were male, and 47.8% were female. In study 2019nCoV-501, 57.2% of participants were male and 42.3% were female.

Subgroup analyses by sex were performed for solicited TEAEs in Clinical Study 2019nCoV-301 and 2019nCoV-302. Male participants reported lower frequencies of solicited AEs among both NVX-CoV2373 and placebo recipients after each vaccination than in female participants. The difference between the rates in the NVX-CoV2373 and placebo groups for both males and females are very similar after dose 1 and dose 2 considering both local as well as systemic reactions. Solicited reactions by sex as observed in 2019nCoV-301 are presented in Table 33 (local) and Table 34 (systemic).

Table 33 . Subgroup Analysis of Solicited Local Adverse Events within 7 Days after Dose 1 and Dose 2 by Sex (Safety Analysis Set, 2019nCoV-301)

Subgroup	Any Grade		Grade 3+	
	NVX-CoV2373	Placebo	NVX-CoV2373	Placebo
All participants				
Dose 1	10475/18072 (58.0%)	1881/8904 (21.1%)	198/18072 (1.1%)	23/8904 (0.3%)
Dose 2	13525/17139 (78.9%)	1797/8278 (21.7%)	1147/17139 (6.7%)	26/8278 (0.3%)
Male				
Dose 1	5027/9447 (53.2%)	800/4510 (17.7%)	59/9447 (0.6%)	6/4510 (0.1%)
Dose 2	6609/8926 (74.0%)	779/4188 (18.6%)	405/8926 (4.5%)	7/4188 (0.2%)
Female				
Dose 1	5448/8625 (63.2%)	1081/4394 (24.6%)	139/8625 (1.6%)	17/4394 (0.4%)
Dose 2	6916/8213 (84.2%)	1018/4090 (24.9%)	742/8213 (9.0%)	19/4090 (0.5%)

Table 34.Subgroup Analysis of Solicited Systemic Adverse Events within 7 Days after Dose 1 and Dose 2 by Sex (Safety Analysis Set, 2019nCoV-301)

Subgroup	Any Grade		Grade 3+	
	NVX-CoV2373	Placebo	NVX-CoV2373	Placebo
All participants				
Dose 1	8614/18072 (47.7%)	3562/8904 (40.0%)	439/18072 (2.4%)	188/8904 (2.1%)
Dose 2	11906/17139 (69.5%)	2969/8278 (35.9%)	2077/17139 (12.1%)	170/8278 (2.1%)
Male				
Dose 1	4013/9447 (42.5%)	1620/4510 (35.9%)	164/9447 (1.7%)	54/4510 (1.2%)
Dose 2	5818/8926 (65.2%)	1295/4188 (30.9%)	893/8926 (10.0%)	55/4188 (1.3%)
Female				
Dose 1	4601/8625 (53.3%)	1942/4394 (44.2%)	275/8625 (3.2%)	134/4394 (3.0%)
Dose 2	6088/8213 (74.1%)	1674/4090 (40.9%)	1184/8213 (14.4%)	115/4090 (2.8%)

With regards to unsolicited AEs, including severe AEs, SAEs, MAAEs, and AESIs, there are no clear indications of a differential safety profile with relatively small, non-significant, differences in several SOCs detected but no consistent pattern emerging. Of note, where there are clearly higher rates of certain AEs in males vs females or vice versa this is mostly true for both the NVX-CoV2373 group as well as the placebo group.

By underlying comorbidites

In 2019nCoV-301, participants with co-morbidities of obesity, chronic kidney disease, cardiovascular disease, and diabetes mellitus type 2 reported lower frequencies and intensities of solicited local and systemic AEs after each vaccination among NVX-CoV2373 recipients than the overall study population who received NVX-CoV2373 and participants with chronic lung disease. The frequencies and intensities in participants with chronic lung disease were similar as the overall study population.

By Age

Participants in the older age cohort (≥ 65 years of age) reported lower frequencies and intensities of solicited local and systemic AEs among NVX-CoV2373 recipients after each vaccination than in participants in the younger age cohort (18 to ≤ 64 years of age). An overview of adverse events reported in 2019nCoV-302 stratified by age is presented in Table 35. A similar pattern was observed in study 2019nCoV-301.

Table 35 Overall Summary of adverse events reported in 2019nCoV-302 stratified by age

	Participants 18 to 64 Years		Participants 65 to 84 Years	
	NVX-CoV2373 N = 1121/1106	Placebo N = 1106/1094	NVX-CoV2373 N = 243/242	Placebo N = 244/241
Solicited Adverse Events				
Any local AE				
1st dose	683 (64.4)	244 (23.5)	79 (35.1)	22 (9.4)
2nd dose	823 (83.9)	179 (18.8)	142 (64.0)	20 (9.0)
Any systemic AE				
1st dose	545 (51.6)	423 (40.8)	65 (28.9)	59 (25.0)
2nd dose	666 (68.2)	311 (32.9)	108 (48.9)	48 (21.9)
Unsolicited Adverse Events				
Any TEAEs	1305 (23.7)	1031 (18.7)	497 (24.1)	383 (18.6)
Any severe TEAEs	41 (0.7)	32 (0.6)	17 (0.8)	16 (0.8)
Any treatment-related TEAEs	607 (11.0)	258 (4.7)	212 (10.3)	83 (4.0)
Any severe treatment-related TEAEs	10 (0.2)	2 (<0.1)	3 (0.1)	1 (<0.1)
Any treatment-emergent MAAEs	189 (3.4)	201 (3.6)	96 (4.6)	94 (4.6)
Any serious TEAEs	26 (0.5)	23 (0.4)	15 (0.7)	18 (0.9)
Any AESIs: PIMMC	4 (<0.1)	4 (<0.1)	1 (<0.1)	3 (0.1)
Any AESIs: related to COVID-19	8 (0.1)	20 (0.4)	0	2 (<0.1)

Table 36 . Overall Summary of Participants with Specified Treatment Emergent Adverse Events and Other Categories from After Start of First Vaccination (Day 0) to End of Follow-up for the Pooled Safety Analysis (Safety Analysis Set)

MedDRA Terms – SOC, PTs or Other Non-MedDRA Categories	Age 18 to < 65 years		Age 65 to 74 years		Age 75 to 84 years		Age 85+ years	
	NVX-CoV2373 (n, %) N = 25282	Placebo (n, %) N = 16433	NVX-CoV2373 (n, %) N = 4050	Placebo (n, %) N = 2931	NVX-CoV2373 (n, %) N = 705	Placebo (n, %) N = 514	NVX-CoV2373 (n, %) N = 21	Placebo (n, %) N = 14
Total AEs	**5321 (21.05)**	**2993 (18.21)**	**1059 (26.15)**	**610 (20.81)**	**165 (23.40)**	**103 (20.04)**	**3 (14.29)**	**4 (28.57)**

Table 36 . Overall Summary of Participants with Specified Treatment Emergent Adverse Events and Other Categories from After Start of First Vaccination (Day 0) to End of Follow-up for the Pooled Safety Analysis (Safety Analysis Set)

MedDRA Terms – SOC, PTs or Other Non-MedDRA Categories	Age 18 to < 65 years		Age 65 to 74 years		Age 75 to 84 years		Age 85+ years	
	NVX-CoV2373 (n, %) N = 25282	Placebo (n, %) N = 16433	NVX-CoV2373 (n, %) N = 4050	Placebo (n, %) N = 2931	NVX-CoV2373 (n, %) N = 705	Placebo (n, %) N = 514	NVX-CoV2373 (n, %) N = 21	Placebo (n, %) N = 14
Serious AEs – Total	**163 (0.64)**	**116 (0.71)**	**43 (1.06)**	**28 (0.96)**	**13 (1.84)**	**10 (1.95)**	**0**	**0**
Fatal	7 (0.03)	5 (0.03)	5 (0.12)	2 (0.07)	0	1 (0.19)	0	0
Hospitalization /prolong existing hospitalization	137 (0.54)	100 (0.61)	33 (0.81)	24 (0.82)	12 (1.70)	10 (1.95)	0	0
Life-threatening	18 (0.07)	16 (0.10)	12 (0.30)	4 (0.14)	4 (0.57)	3 (0.58)	0	0
Disability/incapacity	7 (0.03)	5 (0.03)	1 (0.02)	2 (0.07)	0	0	0	0
Other (medically significant)	34 (0.13)	23 (0.14)	11 (0.27)	8 (0.27)	3 (0.43)	0	0	0
AE leading to drop-out	64 (0.25)	21 (0.13)	21 (0.52)	11 (0.38)	3 (0.43)	3 (0.58)	0	0
Psychiatric disorders	203 (0.80)	102 (0.62)	8 (0.20)	13 (0.44)	5 (0.71)	2 (0.39)	0	0
Nervous system disorders	1136 (4.49)	680 (4.14)	209 (5.16)	118 (4.03)	29 (4.11)	18 (3.50)	1 (4.76)	0
Accidents and injuries	349 (1.38)	215 (1.31)	74 (1.83)	44 (1.50)	20 (2.84)	7 (1.36)	1 (4.76)	2 (14.29)
Cardiac disorders	65 (0.26)	37 (0.23)	23 (0.57)	21 (0.72)	7 (0.99)	4 (0.78)	0	0
Vascular disorders	193 (0.76)	111 (0.68)	57 (1.41)	30 (1.02)	11 (1.56)	4 (0.78)	1 (4.76)	0
Cerebrovascular disorders	8 (0.03)	5 (0.03)	4 (0.10)	1 (0.03)	0	0	0	0
Infections and infestations	906 (3.58)	652 (3.97)	153 (3.78)	116 (3.96)	25 (3.55)	23 (4.47)	0	1 (7.14)
Anticholinergic syndrome	0	0	0	0	0	0	0	0
Quality of life decreased	0	0	0	0	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	**170 (0.67)**	**117 (0.71)**	**53 (1.31)**	**27 (0.92)**	**11 (1.56)**	**6 (1.17)**	**1 (4.76)**	**0 (0.00)**
Postural hypotension	2 (< 0.01)	0	3 (0.07)	1 (0.03)	0	0	0	0

Table 36 . Overall Summary of Participants with Specified Treatment Emergent Adverse Events and Other Categories from After Start of First Vaccination (Day 0) to End of Follow-up for the Pooled Safety Analysis (Safety Analysis Set)

MedDRA Terms – SOC, PTs or Other Non-MedDRA Categories	Age 18 to < 65 years		Age 65 to 74 years		Age 75 to 84 years		Age 85+ years	
	NVX-CoV2373 (n, %) N = 25282	Placebo (n, %) N = 16433	NVX-CoV2373 (n, %) N = 4050	Placebo (n, %) N = 2931	NVX-CoV2373 (n, %) N = 705	Placebo (n, %) N = 514	NVX-CoV2373 (n, %) N = 21	Placebo (n, %) N = 14
Falls	17 (0.07)	13 (0.08)	10 (0.25)	8 (0.27)	3 (0.43)	2 (0.39)	1 (4.76)	0
Black outs	0	1 (< 0.01)	0	0	0	1 (0.19)	0	0
Syncope	25 (0.10)	18 (0.11)	4 (0.10)	1 (0.03)	1 (0.14)	0	0	0
Dizziness	81 (0.32)	56 (0.34)	18 (0.44)	13 (0.44)	3 (0.43)	1 (0.19)	0	0
Ataxia	0	0	0	0	0	0	0	0
Fractures	50 (0.20)	30 (0.18)	20 (0.49)	5 (0.17)	5 (0.71)	2 (0.39)	0	0
Other AE appearing more frequently in older patients[1]	**2345 (9.28)**	**1165 (7.09)**	**571 (14.10)**	**239 (8.15)**	**84 (11.91)**	**32 (6.23)**	**1 (4.76)**	**1 (7.14)**
General disorders and administration site conditions								
Fatigue	506 (2.00)	257 (1.56)	106 (2.62)	44 (1.50)	14 (1.99)	7 (1.36)	0	0
Injection site pain	431 (1.70)	89 (0.54)	128 (3.16)	22 (0.75)	17 (2.41)	1 (0.19)	0	1 (7.14)
Injection site erythema	78 (0.31)	13 (0.08)	21 (0.52)	3 (0.10)	4 (0.57)	0	0	0
Injection site pruritus	67 (0.27)	5 (0.03)	23 (0.57)	1 (0.03)	5 (0.71)	0	0	0
Nervous system disorders								
Headache	788 (3.12)	421 (2.56)	131 (3.23)	80 (2.73)	20 (2.84)	10 (1.95)	0	0
Musculoskeletal and connective tissue disorders								
Myalgia	411 (1.63)	117 (0.71)	84 (2.07)	20 (0.68)	12 (1.70)	4 (0.78)	0	0
Pain in extremity	311 (1.23)	73 (0.44)	96 (2.37)	13 (0.44)	13 (1.84)	2 (0.39)	0	0
Arthralgia	156 (0.62)	81 (0.49)	32 (0.79)	29 (0.99)	3 (0.43)	3 (0.58)	0	0
Infections and infestations								
Urinary tract infection	78 (0.31)	58 (0.35)	30 (0.74)	21 (0.72)	3 (0.43)	3 (0.58)	0	0

Table 36 . Overall Summary of Participants with Specified Treatment Emergent Adverse Events and Other Categories from After Start of First Vaccination (Day 0) to End of Follow-up for the Pooled Safety Analysis (Safety Analysis Set)

MedDRA Terms – SOC, PTs or Other Non-MedDRA Categories	Age 18 to < 65 years		Age 65 to 74 years		Age 75 to 84 years		Age 85+ years	
	NVX-CoV2373 (n, %) N = 25282	Placebo (n, %) N = 16433	NVX-CoV2373 (n, %) N = 4050	Placebo (n, %) N = 2931	NVX-CoV2373 (n, %) N = 705	Placebo (n, %) N = 514	NVX-CoV2373 (n, %) N = 21	Placebo (n, %) N = 14
Gastrointestinal disorders								
Diarrhoea	164 (0.65)	137 (0.83)	36 (0.89)	16 (0.55)	3 (0.43)	4 (0.78)	0	0
Respiratory, thoracic and mediastinal disorders								
Oropharyngeal pain	157 (0.62)	138 (0.84)	31 (0.77)	19 (0.65)	4 (0.57)	4 (0.78)	0	0
Rhinorrhoea	110 (0.44)	105 (0.64)	26 (0.64)	19 (0.65)	3 (0.43)	2 (0.39)	0	0
Vascular disorders								
Hypertension	139 (0.55)	88 (0.54)	43 (1.06)	22 (0.75)	8 (1.13)	4 (0.78)	1 (4.76)	0

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; NVX-CoV2373 = 5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant; PT = preferred term; SARS-CoV-2 rS = severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine; SOC = system organ class.

Note: N = number of participants in each treatment group; n = number of participants in each specified category of adverse events; % = (n/N)*100

[1] Frequencies of Unsolicited Adverse Events Reported from After Start of First Vaccination Through 28 Days After Second Vaccination (eg, Day 49) in ≥ 0.5% of Participants of adults ≥ 65 years in the Safety Population, Pooled Analysis of Safety Data (reference Table 2.5-18 of Module 2.5).

By HIV-status

In 2019nCoV-501, approximately 94% of participants were HIV-negative, with a median age of 27.0 years and 4.4% aged 65 years and older. An overview of unsolicited adverse events by HIV-status is presented in Table 44.

Table 37 . Overall Summary of unsolicited adverse events reported in 2019nCoV-501 in Healthy HIV-Negative and Medically Stable HIV-Positive Participants Regardless of Baseline Serostatus (Safety Analysis Set)

	HIV-negative		HIV-positive	
	NVX-CoV2373 N = 2089	Placebo N = 2075	NVX-CoV2373 N = 122	Placebo N = 122
Any TEAEs	312 (14.9)	309 (14.9)	17 (13.9)	18 (14.8)
Any severe TEAEs	14 (0.7)	16 (0.8)	1 (0.8)	2 (1.6)
Any treatment-related TEAEs	67 (3.2)	46 (2.2)	3 (2.5)	5 (4.1)
Any severe treatment-related TEAEs	2 (< 0.1)	1 (< 0.1)	0	0
Any treatment-emergent MAAEs	20 (1.0)	18 (0.9)	3 (2.5)	4 (3.3)
Any serious TEAEs	6 (0.3)	8 (0.4)	0	2 (1.6)
Any AESIs: PIMMC	0	0	0	0

Any AESIs: related to COVID-19	11 (0.5)	13 (0.6)	0	1 (0.8)

Abbreviations: AESI = adverse events of special interest; COVID-19 = coronavirus disease 2019; MAAE = medically attended adverse events; NVX-CoV2373 = 5 µg SARS-CoV-2 rS with 50 µg Matrix-M1 adjuvant; PIMMC = potential immune-mediated medical conditions; SARS-CoV-2 rS = severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine; TEAE = treatment-emergent adverse event.

By serostatus at baseline

In study 2019nCoV-501, negative baseline serostatus and positive baseline serostatus for SARS-CoV-2 were established, respectively, for 65.9% and 34.1% of participants. As can be seen in Table 45 rates of solicited and unsolicited adverse events were similar in subjects seropositive or seronegative at baseline. Similarly, in 2019nCoV-302 – where only 4.2% of participants was seropositive at baseline - there was no suggestion of an increase in reactions or TEAEs in seropositive persons vs seronegative persons.

Table 38 Overall Summary of adverse events reported in 2019nCoV-501 stratified by serostatus at baseline (Safety analysis set)

	Baseline Seronegative		Baseline seropositive	
	NVX-CoV2373 1476/1428	Placebo 1427/1377	NVX-CoV2373 735/712	Placebo 770/743
Solicited Adverse Events				
Any local AE				
1st dose	447 (30.3)	210 (14.7)	212 (28.8)	110 (14.3)
2nd dose	418 (29.3)	142 (10.3)	198 (27.8)	83 (11.1)
Any systemic AE				
1st dose	421 (28.5)	345 (24.2)	211 (28.7)	197 (25.6)
2nd dose	348 (24.4)	239 (17.3)	168 (23.6)	127 (17.0)
Unsolicited Adverse Events				
Any TEAEs	214 (14.5)	201 (14.1)	115 (15.6)	126 (16.4)
Any severe TEAEs	6 (0.4)	15 (1.1)	9 (1.2)	3 (0.4)
Any treatment-related TEAEs	49 (3.3)	35 (2.5)	21 (2.9)	16 (2.1)
Any severe treatment-related TEAEs	1 (< 0.1)	0	1 (0.1)	1 (0.1)
Any treatment-emergent MAAEs	15 (1.0)	13 (0.9)	8 (1.1)	9 (1.2)
Any serious TEAEs	6 (0.4)	14 (1.0)	5 (0.7)	4 (0.5)
Any AESIs: PIMMC	0	0	0	0
Any AESIs: related to COVID-19	9 (0.6)	5 (0.4)	2 (0.3)	9 (1.2)

In pregnancy and during breastfeeding

There is limited experience with NVX-CoV2373 in pregnancy. A total of 137 pregnancies were reported in the clinical development program as of 26 October 2021. Of these participants, 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.

2.6.8.6. Immunological events

In order to evaluate the occurrence of potential hypersensitivity reactions following administration of the vaccine, the SMQ of Hypersensitivity (Narrow) was run across the pooled studies included in the Integrated Safety Summary (Studies 2019nCoV-101 Part 1, 2019nCoV-101 Part 2, 2019nCoV-301,

2019nCoV-302, and 2019nCoV-501). Events occurring within the 3 days of vaccination were captured. Across the studies, 113 (0.38%) vaccine recipients compared to 42 (0.21%) placebo recipients reported AEs under the Hypersensitivity SMQ Narrow within the 3 days of vaccination, with a Risk Difference (RD) of 0.20 (95% CI: 0.11, 0.30).

For the SOC Immune System Disorders, the frequency was higher for vaccine recipients (0.04%) than for placebo recipients (0.00%) with 8 (0.03%) recipients reporting of allergy to vaccine and 3 (< 0.01%) recipients reporting hypersensitivity. None of the three hypersensitivity events are considered related to NVX-CoV2373. None of the three hypersensitivity events are considered related to NVX-CoV2373. Upon review of the narratives of the 8 reports of 'allergy to the vaccine', it was found that 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. No events of anaphylaxis have been reported.

2.6.8.7. Safety related to drug-drug interactions and other interactions

Local and systemic reactions were higher in participants included in the Seasonal Influenza Substudy**,** who received concomitant influenza vaccine, than in participants who did not receive concomitant influenza vaccine.

- Following first dose, where concomitant influenza vaccination did occur, there was a higher frequency of solicited local AEs in the NVX-CoV2373 group who received concomitant influenza vaccine (70.1%) than in those who received only NVX-CoV2373 (57.6%). Systemic reactions were reported by 60.1% in the Seasonal Influenza Substudy, compared to 45.7% in those who did not receive concomitant influenza vaccine.
- Following second vaccination (where concomitant influenza vaccination did not occur), the frequency of solicited local AEs in participants in the Seasonal Influenza Substudy was 85.0%, compared to 79.6% in subjects not included in the Seasonal Influenza Substudy. Systemic reactions were reported by 69.7% compared to 64.0% respectively.

2.6.8.8. Discontinuation due to adverse events

2019nCoV-301

Study discontinuations due to adverse events were reported by a total of 24 subjects (0.1%), 17 (0.1%, 65 events) in the NVX-CoV2373 arm and 7 (0.1%, 14 events) in the placebo arm. IRs of unsolicited TEAEs resulting in study discontinuation reported from start of first vaccination to blinded crossover or EoS with > 0.05 e/100 PY in the NVX-CoV2373 group was fatigue (0.06 vs 0). Adverse events resulting in vaccine discontinuation were reported by 57 (0.3%) subjects in the NVX-CoV2373 arm and 16 (0.2%) subjects in the placebo arm.

2019nCoV-302

TEAEs leading to study discontinuation were recorded for 27 (0.4%) of subjects in the NVX-CoV2373 group and 17 (0.2%) subjects in the placebo group. Treatment-related TEAEs leading to study discontinuation were reported in 14 (0.2%) subjects in the NVX-CoV2373 group and 3 (<0.1%) in the placebo group. The most frequent (incidence > 1 participant) treatment-related TEAEs leading to study discontinuation in the NVX-CoV2373 group were injection site pain (4 participants) and myalgia (2).

There were similar frequencies of participants reporting unsolicited TEAEs leading to discontinuation of study vaccine between the 2 study vaccine groups, with 30 (0.4%) participants in the NVX-CoV2373 group and 23 (0.3%) participants in the placebo group.

2019nCoV-501

Unsolicited TEAEs resulting in vaccine discontinuation were reported in 0 of 2,211 participants in the NVX-CoV2373 group versus 1 (< 0.1%) of 2,197 participants in the placebo group; 4 (0.2%) of 2,211 participants in the NVX-CoV2373 group and 4 (0.2%) of 2,197 participants in the placebo group reported TEAEs resulting in study discontinuation.

2.6.9. Discussion on clinical safety

Methods

Safety data was collected in 4 studies conducted in Australia, the US, South Africa, the UK and Mexico. A pooled analysis of safety data from these studies has been presented, including data from the first vaccination up to the data cut-off, blinded cross over or study unblinding.

Methods for the collection and reporting of safety data appear largely appropriate.

There is an apparent different pattern in reactions as observed in study 2019nCoV-501 compared to studies -301 and -302. In 2019nCoV-501 lower rates of local and systemic reactions were reported, and the rates were reduced following the second dose compared to the first. Further, reactions were less often severe as compared to the other clinical trials. As the reason for the discrepancy between the studies in reporting is not clear, the rates of reactions as presented in the SmPC has been based on 2019nCoV-301 and 2019nCoV-302 and does not consider the data of study 2019nCoV-501. It is however anyhow considered that pivotal studies -302 and -301 are sufficiently large and of adequate methodology to characterise the reactogenicity profile. Of note, the reactogenicity subset in study -302 included participants who received concomitant influenza vaccine. This is considered acceptable as it is a conservative approach: participants who received concomitant influenza vaccine reported more reactions (approximately 10-15% higher rates of local reactions).

Solicited AEs were collected for 7 days post dose 1 and post dose 2. Unsolicited AEs were collected up to 28 days after the second dose, with the exception of SAEs, MAAEs and AESIs which were collected during the entire study period, which was considered appropriate.

Exposure

At the time of the analysis, a total of 49,950 participants age 18 years and older received at least one dose of NVX-CoV2373 (n=30,058) or placebo (n=19,892). Over 96% of participants have received two doses. Median exposure from the second dose was 90 days in study 2019nCoV-302 and 76/77 days in the NVX-CoV2373 and placebo group respectively in study 2019nCoV-301, with 66% of participants completing at least 2 months follow-up. The median duration of follow-up in the pooled safety database was 70 days post-Dose 2. The shorter median duration of follow-up in the pooled data as compared to the individual studies is due to censoring at unblinding.

Adverse Events

Reactogenicity was evaluated in 1,364 participants who received a first dose and 1,348 participants who received a second dose of NVX-CoV2373 in study 2019nCoV-302, and 19,729 participants who received a first dose and 17,139 participants who received a second dose of NVX-CoV2373 in study 2019nCoV-301.

In both studies, there were more solicited local and systemic reactions reported by participants in the NVX-CoV2373 group compared to placebo, with the frequency and intensity of reactions increasing with the second dose compared to the first.

Pain and tenderness were the most commonly reported *local reactions* in both study 2019nCov-302 as study 2019nCov-301. Pain was reported by 34% after the first dose of NVX-CoV2373 and 59% after the second dose. Tenderness was reported by 53% post dose 1 and 74% post dose 2. In the placebo group rates were between 11% and 17% and did not increase with the second dose. Local reactions were mostly mild to moderate, with 1.1% of participants in the NVX-CoV2373 group reporting grade 3 local reactions after the first dose in either study and 6.6% after the second dose. Local reactions pain and tenderness had a median duration of 1 to 2 days after the first dose and 2 to 3 days after the second dose.

Headache, fatigue, and muscle pain were the most frequent *solicited systemic AEs*, reported by 25%, 25%, and 23% post dose 1 compared to 23%, 22%, and 13% in the placebo group respectively, and by 44%, 49%, and 48% post dose 2 compared to 19%, 21%, and 12% in the placebo group. The median duration of headache, fatigue and muscle pain was 1 day after each dose in both studies. For GI reactions (nausea/ vomiting), after the first dose rates are comparable between the NVX-CoV2373 group and the placebo group, however with the second dose reported nausea/vomiting doubled in the vaccine group.

Fever was reported infrequently, but again increased substantially with the second dose in the NVX-CoV2373 group (in study -302 from 2.3% to 5.1%, in -301 from 0.4 to 5.7%).

Overall, concomitant analgesic medication use was low, varying from < 1% to 3% depending on study and dose.

Systemic reactions were mostly mild with 1.3%-2.3% reporting grade 3 systemic reactions after the first dose, and 6.8%-12.0% reporting grade 3 systemic reactions following the second dose. Grade 4 reactions were reported by 0.1% in study 2019nCov-301.

Unsolicited AEs

There were higher frequencies of unsolicited TEAEs within the 49 days after first vaccination (28 days after the second dose) among NVX-CoV2373 recipients than among placebo recipients overall (23.8% vs 18.7% in study -302 and 16.3% vs 14.8% in -301). The imbalance between the NVX-CoV2373 group and the placebo group in study 2019nCoV-302 was mainly driven by the SOC of general disorders and administration site conditions (n=438, 5.8%, vs n=191, 2.5%). Also, there were more cases of lethargy (SoC: Nervous system disorders) reported in the NVX-CoV2373 group (n=77 (1.0%) vs n=29 (0.4%)). A similar picture is observed in study 2019nCoV-301 and 2019nCoV-501.

In the clinical trials there is a signal of increased risk of hypertension following NVX-CoV2373 as compared to the placebo group. There was an imbalance in severe cases of hypertension in trial 2019nCoV-302 where 13 vs 3 severe TEAEs were reported related to hypertension as well as four events of hypertension and hypertensive crisis reported as an SAE in the NVX-CoV2373 group, compared to 1 in the placebo group. No further information is available on the severity of reported events nor on the duration. There was no standardised assessment of hypertension in the trials, and there is limited information on the episodes of hypertension or worsening of hypertension reported. Further, it is unclear if an AE of hypertension was accompanied by measurement of the blood pressure (BP) at multiple timepoints or reflects an increase at a single timepoint. Therefore, it is not possible to determine the potential impact of the observed increased risk for vaccinees and whether there is any cause for concern. With regards to a mechanism, hypertension could be related to anxiety surrounding the vaccination (in which case similar rates would be expected in the placebo group) or possibly related to an inflammatory reaction to the vaccine. Despite these limitations it is deemed relevant to inform

prescribers of the increased risk as observed in the clinical trials and based on the higher incidence in the NVX-CoV2373 vaccinated participants, which was included in the table of ADRs in section 4.8 of the SmPC. Further, more information should be actively collected by the participant to further characterise the risk of hypertension following vaccination either through monitoring of BP in older adults still to be vaccinated in ongoing trials or through prospective observational studies in persons at risk of hypertension, where close and consistent monitoring of blood pressure can take place.

There were no relevant imbalances or signals with regards to Adverse Events of Special Interest in studies -2019nCov-302, 2019nCov-501, and 2019nCov-101, however in study 2019nCov-301 there was an increase in the incidence of PIMMCs reported in the NVX-CoV2373 group. The type of events reported are diverse, with no clear patterns emerging aside from the overall imbalance. Whilst exploring this signal, the applicant conducted a MedDRA SMQ which identified additional events in both treatment groups not reported by investigators. This analysis did not suggest an imbalance. In addition, the applicant provided a review of PIMMMCs in different SOCs based on the entire clinical safety database. In the SOCs of Skin and Subcutaneous Tissue Disorders, Eye Disorders and Endocrine Disorders there is a risk difference suggesting increased risk in the NVX-CoV2373 group however differences are small, there is no clear association with a single PT, and therefore these imbalances may be due to chance. Where background rates are available, the observed cases do not seem to be higher although no adequate analysis comparing rates following vaccination with expected background rates was submitted.

The clinical trial data from 2019nCoV-301 provide a suggestion of a higher risk of AEs related to inflammation of the eye following vaccination with NVX-CoV2373. This increased risk is not detected in other trials and is based on small numbers; therefore, it is not clear whether it is indeed related to NVX-CoV2373. It is considered that the reporting of AEs related to eye inflammation, including but not limited to uveitis, iridocyclitis, iritis, lacrimation increased, eye(lid) swelling, diplopia, photophobia, should be closely followed in the Monthly Safety Summary Reports/PSURs.

In 2019nCoV-301 also show an increased reporting of AEs in the SOC of Reproductive and breast disorders, which is explained by imbalances in PTs of dysmenorrhoea (12 vs 3) and menstruation irregular (5 vs 0). As there were no adverse events reported in relation to these PTs in study -302, and as there is no clear pattern in time to onset and factors in the medical history that may have contributed, it is not clear based on the available evidence whether NVX-CoV2373 may be related to these events. Therefore, it is recommended that menstrual disorders are followed in the MSSRs/PSURs.

Deaths and other serious adverse events

There were 3 deaths in study 2019nCoV-302, 13 deaths in -301, and 4 deaths in -501. None were considered related to study vaccine. Whilst it is agreed that none of the deaths are related to study vaccine, there were two deaths due to COVID-19 pneumonia in the vaccine group. Onset of symptoms was 8 days and 19 days after the first dose.

There were no imbalances in SAEs between the vaccine groups in study 2019nCoV-302 or 2019nCoV-501. In study 2019nCoV-301, there are imbalances between the treatment groups in the reporting of SAEs. There were numerically more SAEs in the SOC of Hepatobiliary Disorders, mainly driven by events related to cholecystitis (9 vs 0). Further, there were more events of prostate cancer (5 vs 0), cerebrovascular accident (7 vs 1) and hypertension/hypertensive crisis (6 vs 0) in the NVX-CoV2373 treatment group. Differences remain when incidence rates were compared therefore the longer duration of follow up time due to higher levels of unblinding in the placebo group do not fully explain the imbalances.

The mechanism behind vaccine induced cholecystitis occurring within a relatively short timeframe after vaccination is unclear although may be attributable to the activation of the inflammatory system. All cases of cholecystitis were in participants with underlying risk factors (e.g. female, gallstones, obese). There was no consistent pattern in time to onset in the reported cases, varying from 6 to 64 days after the last dose. Further, the data presented by the applicant suggest a relatively high background rate although the number of cases expected within the clinical trials is unclear. As there is a numerical imbalance between the vaccine and placebo group, and as all cases are considered serious, although there is currently insufficient evidence to conclude that cholecystitis is possibly related to NVX-CoV2373 the recommendation is to follow cholecystitis in the MSSRs/PSURs.

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, 'prostate cancer' is unlikely related to NVX-CoV2373.

The events of '*cerebrovascular accident'* occurred in participants with pre-existing medical conditions were known risk factors for stroke, including diabetes mellitus, hypertension, tobacco abuse, hyperlipidaemia, atrial fibrillation, recent myocardial infarction, and obesity. There was no clear pattern in the time between last vaccine dose and onset of symptoms. Despite the absence of any clear indication that the observed cases were related to the vaccine and any clear indication of an increased risk of CVA and/or related conditions with NVX-CoV2373, due to the imbalance between the two groups in 2019nCoV-301 it is recommended that CVA and related conditions are monitored in the MSSRs/PSURs.

In study -302, an SAE in the NVX-CoV2373 group of myocarditis was considered related to study vaccine by the investigator, in a 18-29 yoa study participant with no relevant risk factors. Important to note that a viral aetiology cannot be excluded based on the available information. A further four cases were identified during the vaccination cross over period, including two cases of pericarditis. For two cases – an event of myocarditis and an event of myocarditis/pericarditis - considering the TTO, a relation is possible although here potential confounders are present which could provide an alternative explanation (strep throat, viral syndrome and the latter preceding lower respiratory tract infection with elevated WBC and CRP). It will be important to carefully monitor and assess the risk of myocarditis/pericarditis following vaccination and it should be included as an important potential risk in the Safety Specifications of the Risk Management Plan **(RMP).**

Laboratory values

Clinical laboratory findings were only reported for study 2019nCoV-101 (Part 1), where haematology and serum chemistry was part of the safety assessments. According to the protocols of studies 2019nCOV-101 (Part 2), -302 and -501 it appears that the effects of vaccination on clinical laboratory values (i.e. haematology, serum chemistry) has not been evaluated within these studies.

There were similar rates of laboratory investigation TEAEs for NVX-CoV2373 compared with placebo. TEAEs in most PTs were infrequent, with less than two events for most PTs in either the NVX-CoV2373 or placebo groups; there were no clear imbalances between the NVX-CoV2373 group and placebo.

Safety in special populations

Overall, 47.4% (n=14232) of NVX-CoV2373 recipients in the clinical trials were female and 52.7% (n=15826) were male. Therefore, both sexes are sufficiently represented. There were no relevant differences in the safety profile of NVX-CoV2373 in female and male participants. Whilst higher rates of solicited adverse events were reported by females compared to males, with females reporting approximately 5-10% more solicited reactions after dose 1 and dose 2, this is observed in the NVX-CoV2373 group as well as the placebo group which may indicate that the increased reporting in females is not vaccine related.

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.

There is no clear pattern of a differential safety profile of NVX-CoV2373 by HIV status. Although there is a suggestion of less reactions in HIV-positive participants, this may also be due to age which is known to affect reactogenicity. HIV-negative participants had a median age of 27 years, compared to 38 years in HIV-positive participants. Medically attended AEs were reported more often in HIV positive participants (2.9%) compared to HIV-negative participants (0.9%), at a similar frequency in the placebo as the NVX-CoV2373 group.

Participants with co-morbidities of obesity, chronic kidney disease, cardiovascular disease, and diabetes mellitus type 2 reported lower frequencies and intensities of solicited local and systemic AEs after each vaccination among NVX-CoV2373 recipients compared to the overall study population as well as participants with chronic lung disease.

Considering older adults participating in the trials, reactogenicity was markedly lower in those aged 65-84 years of age compared to those 18-64 years of age. Frequencies of unsolicited AEs were similar in older adults compared to those aged 18-64 years of age, with no difference in related adverse events or serious adverse events. There is a potentially higher rate of medically attended AEs in older adults, however this is consistent between the two treatment groups and may be reflective of different health care seeking behaviour in this demographic rather than a different safety profile of NVX-CoV2373.

There is limited clinical data in pregnant women, with 95 pregnancies reported in the clinical trials of which the majority (60) were still ongoing at the time of reporting. There were no stillbirths or foetal deaths. There are no data available on the safety of NVX-CoV2373 administered during breastfeeding. Preclinical data show no effect of NVX-CoV2373 on the reproductive or developmental parameters. Therefore, no safety issues of use during pregnancy are foreseen. Furthermore, there is no reason to assume that constituents of NVX-CoV2373 will be excreted in breast milk. It is to be expected that anti-SARS-COV2 antibodies elicited by NVX-CoV2373 will be excreted in the colostrum, which may contribute to the protection of the newborn child.

Safety related to drug-drug interactions and other interactions

Concomitant administration with influenza vaccine increased reporting of solicited AEs relative to when NVX-CoV2373 was administered without influenza vaccine. This is reflected in the SmPC.

Immunological events

No events of anaphylaxis have been reported though this likely reflects the rarity of this event in relationship to the size of the pre-authorisation safety database for the vaccine.

Discontinuation due to AES

In general, there were few discontinuations (vaccination/study) due to treatment emergent adverse events. Whilst none of the studies showed an imbalance in the study discontinuations due to AEs per study group, in -301 more events were reported by those that discontinued the study due to AEs in the NVX-CoV2373 group. Further, in both pivotal studies a slightly higher proportion of participants discontinued the vaccination with the imbalance mostly due to reactions to the vaccine (i.e. headache, injection-site pain, myalgia).

2.6.10. Conclusions on the clinical safety

Overall, the safety profile of Nuvaxovid is adequately characterised and appears to be acceptable.

2.7. Risk Management Plan

2.7.1. Safety concerns

The applicant has submitted an RMP including the following summary of safety concerns:

Summary of safety concerns

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

Risks considered important for the inclusion in the summary of safety concerns

Important potential risk

Anaphylaxis, although very rare, it can be life-threatening or fatal, requiring immediate medical attention. The risk of anaphylaxis after all vaccines is estimated to be 1.31 per million vaccine doses. Events of anaphylaxis have been reported with other COVID-19 vaccines. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine.

There were no reports of anaphylaxis in the NVX-CoV2373 clinical development programme. One event of angioedema was reported and was considered as related to the vaccine. Anaphylaxis can manifest clinically with dyspnea, hypotension, swelling (sometimes leading to airway compromise), and rash, and may be life threatening.

Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD): Vaccine-associated enhanced disease (including VAERD) may present as severe disease or modified/unusual clinical manifestations of a known disease presentation and may involve one or multiple organ systems. Subjects with VAED/VAERD may experience rapid clinical deterioration and will likely require non-invasive or invasive mechanical ventilation; and patients diagnosed with acute respiratory distress syndrome (ARDS) have poorer prognosis and potentially higher mortality rate. No cases have been reported at the moment in the current NVX-CoV2373 clinical development.

Myocarditis and pericarditis: Myocarditis and pericarditis are events which may be serious or non-serious and are generally mild but may be potentially life-threatening. Balanced with the risk of death and illness (including myocarditis) seen with COVID-19 itself, the impact on the benefit-risk balance of the vaccine is considered minimal. Two cases of myocarditis were reported following exposure to NVX-CoV2373 and one case was reported following exposure to placebo. In the post-crossover phase of the

studies 301 and 302, three cases of myocarditis were reported. In one case, myocarditis was reported with temporal association to NVX-CoV2373. In the absence of alternative aetiologies, a causal association with the vaccine cannot be excluded in this case. For the other cases, alternative explanations that could explain the event have been reported. Considering that myocarditis and pericarditis has been observed following other COVID-19 vaccines, it is considered that there is a scientific basis for suspicion of a causal relation, although this is not confirmed. It should be listed as important potential risk.

Missing information

Use in pregnancy and while breastfeeding: Pregnant and breastfeeding women are typically excluded from initial clinical trials. There is limited experience with use of NVX-CoV2373 in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition, or post-natal development. Administration of Nuvaxovid in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and foetus. It is unknown whether Nuvaxovid is excreted in human milk. No effects on the breast-fed newborn/infant are anticipated since the systemic exposure of the breast-feeding woman to Nuvaxovid is negligible. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

Use in immunocompromised patients: Immunocompromised individuals are at greater risk of morbidity and mortality from vaccine-preventable disease. In addition, vaccines may be less effective in severely immunocompromised patients, as the vaccinees weakened immune system may not mount a sufficient response. Although there is no evidence that the safety profile of this population receiving NVX-CoV2373 will be different to that of the general population, the possibility cannot be excluded.

Use in frail patients with comorbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders): Frail (unstable) patients with comorbidities are at risk of developing a more severe manifestation of COVID-19. Although there is no evidence that the safety profile of this population receiving NVX-CoV2373 will be different to that of the general population, the possibility cannot be excluded.

Use in patients with autoimmune or inflammatory disorders: There is limited information on the safety of the vaccine in patients with autoimmune or inflammatory disorders. There is no evidence from NVX-CoV2373 clinical studies to date that the safety profile of this population differs with that of the general population. However, given the paucity of data, the possibility cannot be excluded.

Interaction with other vaccines: The safety, immunogenicity, and efficacy of NVX-CoV2373 when co-administered with another vaccine (i.e., with seasonal illness vaccines [such as the influenza vaccines]) was evaluated in approximately 400 persons in the UK Phase 3 study. The binding antibody response to SARS CoV-2 was lower when NVX-CoV2373 was given concomitantly with inactivated influenza vaccine. The clinical significance of this is unknown.

Long-term safety: Given the nature of the NVX-CoV2373 clinical development programme, understanding of the long-term safety profile of NVX-CoV2373 is currently limited.

Risks not considered important for inclusion in the summary of safety concerns

The reactogenicity is in line with what can be expected from a vaccine, and it is considered acceptable to not include those events in the list of safety specifications.

Vaccination errors may relate to administration, vaccination scheme, storage conditions, or errors associated with multidose vials. Furthermore, there is potential for confusion or interchangeability with other COVID-19 vaccines. These potential vaccination errors are mitigated through a number of routine risk minimisation measures, including product information, vaccination reminder cards and medical information contacts.

Adverse Events of Special Interest: The List of AESI is drawn from efforts by regulatory authorities, internationally recognised collaborations, and the scientific literature to identify AESI for vaccinations, and COVID-19 vaccinations specifically. NVX-CoV2373 list of AESIs is provided in the RMP.

Conclusions on the safety specification

It is agreed that the list of safety concerns in the RMP are appropriate.

2.7.2. Pharmacovigilance plan

Routine Pharmacovigilance Activities

The applicant will follow standard pharmacovigilance processes, along with the additional actions referenced in the EU-RMP.

Signal detection and other routine pharmacovigilance activities

The detection of signals described in the NVX-CoV2373 Pharmacovigilance Signaling System (PvSS) plan involves qualitative and quantitative pharmacovigilance methods. The primary data sources for signal detection and the minimum frequency of review are outlined below.

Activity/Data Source	Frequency of Review
Qualitative Data Review	
ICSR (Individual Case Safety Report) medical review of serious cases	Each business day
Review of signal notifications	Each business day
Literature review of EMBASE including Medline	Weekly
Line listing review of adverse event reports from the safety database	Weekly
SMQs (MedDRA [Medical Dictionary tor Regulatory Activities] queries) and targeted PT searches	Weekly
Review of Novavax's post-authorisation Safety Database, including all spontaneous and solicited ICSRs, Medicines and Healthcare products Regulatory Agency (MHRA), Eudravigilance Data Analysis System (EVDAS), and other regulatory databases, as required **	Weekly
US Vaccine Adverse Event Reporting System (VAERS) disproportionality comparisons*	Bi-weekly
EVDAS Electronic Monitoring (eRMR)* **	Bi-weekly
Aggregate review of Novavax's Clinical Trial Database	Monthly
Batch trend analysis	Monthly
Review of Pharmacovigilance Risk Assessment Committee (PRAC) recommendations on signals**	Monthly
Quantitative Data Review	
Trends over time/frequency analysis	Weekly
Disproportionality analysis using EVDAS	Bi-weekly
Disproportionality analysis using VAERS	Bi-weekly
Observed versus expected (O/E) analysis	Monthly

* Applicable once Novavax post-authorisation database reaches a threshold number of ICSRs.

** Applicable once product is authorised in the EU.

Monthly Summary Safety Reports (MSSRs)

In line with EMA's 'Consideration on core requirements for RMPs of COVID-19 vaccines' guidance, the applicant will submit monthly safety reports containing a review of safety information received during the reporting interval, as well as cumulative data. Topics covered by the monthly summary safety reports will include, at a minimum:

- Interval and cumulative number of reports overall and stratified by age groups, report type (medically confirmed vs. non-medically confirmed), seriousness, and in special populations (e.g., pregnant women)
- Interval and cumulative number of reports per HLT and SOC
- Reports per EU country
- Exposure data based on administered doses whenever possible, stratified by region (and within the EU also by country), by age groups, gender, by first vs. second dose
- Safety-related changes to the reference safety information and actions taken in the interval
- List of ongoing and closed signals in the interval, including a summary of their evaluation; reviews of signals identified during the period or of safety topics identified by EMA and requested to be addressed in the MSSR

- Summaries of reported cases of all AESIs and RMP safety concerns: report numbers and relevant cases, including O/E analysis (when possible)
- Fatal reports- numbers and relevant cases (considering co-morbidities and frailty), including O/E analyses (when possible), stratified by age groups.
- Medication errors, if a pattern of errors leading to harm is identified and/or risk minimisation activities are considered warranted
- Details of the search strategy, case definitions, and methodology for O/E analyses including source of background rates, risk windows, etc., as needed
- Benefit-risk considerations

In addition, based on the impurity levels, the applicant should monitor the reactogenicity profile for the secondary dose and for future potential booster injections via routine pharmacovigilance, including the provision of updates as part of the MSSR.

Following the safety clinical assessment of the conditional marketing authorisation, the following events are to be reviewed via routine pharmacovigilance in the MSSR/PSUR: menstrual disorders, cholecystitis, cerebrovascular accidents and related conditions and adverse events related to eye inflammation, including but not limited to uveitis, iridocyclitis, iritis, lacrimation increased, eye(lid) swelling, diplopia, photophobia.

Traceability

To facilitate the traceability of the use of this vaccine, the SmPC includes instructions for HCPs to record the name and batch number of the administered vaccine for each recipient.

Traceability is available for every shipping container of COVID-19 vaccine, which are outfitted with a unique device that provides real-time monitoring of geographic location and records temperature 24 hours per day, 7 days per week while in transit. Each device will also trace the batch/lot of the associated shipment. The device is activated prior to shipment and information is transmitted wirelessly to Novavax at a predefined cadence, until delivery to the customer. A shipment quality report that indicates if the product is acceptable for immediate use is generated by Novavax and transmitted to the vaccinator's practice site upon pressing of the stop button on the data logger, or arrival notification from the carrier in combination with the data logger's location and/or light signal. Additionally, alarms and escalation/notification for excursions (per pre-defined specifications) are programmed into the device.

The carton, which is the lowest saleable unit of the product, is assigned a unique serial number that is linked to information about the product's origin, batch number and expiration date. Each carton contains the product global trade identification number (GTIN), serial number, lot/batch number, and expiry date printed as human readable information and a scannable GS1 2D DataMatrix code.

Further, vaccination reminder cards will be available to member states, if requested, for use by member state vaccinators at the time of vaccination. The vaccination reminder cards contain the following elements:

- Placeholder space for the vaccinee name;
- Placeholder space for the name of the vaccine (brand name) and manufacturer of the vaccine;
- Placeholder space for the batch/lot number of the vaccine;
- Placeholder space for the date the vaccine was administered;

- A reminder to return for the second dose of the vaccine;
- Placeholder spaces for the second dose of the vaccine including the name of the vaccine/manufacturer of the vaccine, batch number, and date of the second dose of the vaccine;
- Novavax website and QR code that links to NovavaxCovidVaccine.com; and
- Information on AE reporting to the member state local health authorities.

In addition to the vaccination reminder cards, traceability labels (two labels per dose) containing product identifier (brand name) and batch/lot information as human readable and GTIN, batch/lot information and expiration date encoded in GS-1 compliant 2-D data matrix will be made available to support documentation of the batch/lot traceability on the vaccination reminder card and for use in the vaccinee's medical records. We also acknowledge that some EU member states may require utilisation of nationally mandated vaccination cards or electronic systems to document batch/lot number; therefore, the available traceability and vaccination reminder cards and/or stickers with printed lot/batch information may not be utilised in all member states.

Specific AE follow-up forms for the following safety concerns:

Two specific adverse reaction **follow up questionnaires** will be used to collect follow-up information on reports of anaphylaxis and Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)

Additional pharmacovigilance activities

The applicant proposes the **following 10 studies** to further evaluate safety and effectiveness, and to address missing information in the post-marketing setting. There are five interventional studies and five non-interventional studies (five safety and two on effectiveness).

The following Table outlines proposed additional pharmacovigilance activities in RMP version 1

Ongoing and Planned Additional Pharmacovigilance Activities

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Not applicable.				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable.				
Category 3 – Required additional pharmacovigilance activities				
Study 2019nCoV-101 (Part 1) Ongoing	To evaluate the safety and immunogenicity of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine (SARS-CoV-2 rS) with or without	Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) Anaphylaxis	Final CSR	31 March 2022

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	Matrix-M adjuvant in healthy subjects.	Myocarditis and pericarditis Long-term safety		
Study 2019nCoV-101 (Part 2) Ongoing	To identify the optimal dose across age strata based on immune response (IgG antibody to SARS-CoV-2 rS) at Day 35 and whether baseline immune status has an impact. To accumulate a safety experience for the candidate vaccine in healthy adult participants based on solicited short-term reactogenicity across a broad age spectrum (by toxicity grade) and by AE profile for primary vaccination (through Day 35). Identify dose(s) to potentially take forward in an EUA setting and/or for Phase 3 efficacy or effectiveness trial(s).	Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) Anaphylaxis Myocarditis and pericarditis Long-term safety	Final CSR	31 December 2022
Study 2019nCoV-501 Ongoing	To evaluate the efficacy, immunogenicity, and safety of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine (SARS-CoV-2 rS) with Matrix-M adjuvant in South African adult subjects living without HIV; and safety and immunogenicity in adults living with HIV.	Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) Anaphylaxis Myocarditis and pericarditis Use in immunocompromised patients Long-term safety	Final CSR	31 December 2022
Study 2019nCoV-302 Ongoing	To evaluate the efficacy and safety of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine (SARS-CoV-2 rS) with Matrix-M adjuvant in adult	Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) Anaphylaxis	Final CSR	31 December 2022

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	participants 18-84 years of age in the UK.	Myocarditis and pericarditis Use in immunocompromised patients Interaction with other vaccines Long-term safety		
Study 2019nCoV-301 Ongoing	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).	Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) Anaphylaxis Myocarditis and pericarditis Use in immunocompromised patients Use in patients with autoimmune or inflammatory disorders Long-term safety	Final CSR	30 September 2023
Study 2019nCoV-402 UK Post-Authorisation Safety Study Using the Clinical Practice Research Datalink (CPRD) Planned	• Evaluate any increased risk of select safety outcomes of interest following vaccination. • Describe and characterise the safety profile of Nuvaxovid. • Evaluate any differences in the risk of safety outcomes by characteristics such as age, sex, race/ethnicity, comorbidities/coinfections, prior COVID-19 infection, concomitant vaccinations, concomitant medications, and/or	Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) Anaphylaxis Myocarditis and pericarditis Use in immunocompromised patients Use in frail patients with co-morbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)	Protocol submission	31 March 2022
			Progress reports	30 June 2023 and 30 June 2024
			Final study report	30 June 2025

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	other characteristics.	Use in patients with autoimmune or inflammatory disorders Interaction with other vaccines Long-term safety		
Study 2019nCoV-405 Global Safety Surveillance Study of Pregnancy and Infant Outcomes Study Using C-VIPER Planned	• Describe and characterise the population of pregnant women who are vaccinated with Nuvaxovid. • Estimate the frequency of select adverse pregnancy outcomes • Estimate the frequency of select adverse foetal/neonatal/infant outcomes at birth and up to the first 12 months of life • Compare the frequency of each safety event of interest between pregnant women (or infants born to these pregnancies) who were exposed to Nuvaxovid and those who were not exposed. • Assess whether the frequency of pregnancy and infant outcomes following vaccination with Nuvaxovid differs by age, sex, race/ethnicity, comorbidities/coinfections, prior COVID-19 infection, concomitant vaccinations, concomitant medications, and/or other characteristics.	Use in pregnancy and while breastfeeding	Protocol submission	31 March 2022
			Progress reports	30 June 2023, 30 June 2024, 30 June 2025, 30 June 2026
			Final study report	30 June 2027

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Study 2019nCoV-404 US Post-authorization safety study using a claims and/or EHR database Planned	• To evaluate the pooled risk of select AESIs within specified time periods after vaccination with the Novavax COVID-19 vaccine, compared to risk during all other times after COVID-19 vaccination within the same individual (self-controlled design), or compared to unvaccinated individuals or those who received an alternative COVID-19 vaccine (comparative cohort study design) • To evaluate whether the risk of AESIs following vaccination with the Novavax COVID-19 vaccine differs by vaccine dose and characteristics such as age, sex, race/ethnicity, comorbidities/coinfections, prior SARS-CoV-2 infection, concomitant vaccinations, concomitant medications, and/or other characteristics.	Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) Anaphylaxis Myocarditis and pericarditis Use in immunocompromised patients Use in frail patients with co-morbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders Interaction with other vaccines Long-term safety	Protocol submission	30 June 2022
			Progress reports	30 September 2023, 30 September 2024
			Final study report	30 September 2025

Planned effectiveness studies (required additional pharmacovigilance activities)

Study/Status	Summary of objectives	Effectiveness uncertainties addressed	Milestones	Due dates
Study 2019nCoV-401 EU/EEA Post-Authorisation Effectiveness Study Based on a Test-Negative Design Using the COVIDRIVE Platform Planned	• Estimate the effectiveness of Nuvaxovid against COVID-19 hospitalisations confirmed by RT-PCR, after adjusting for potential confounders • Estimate the effectiveness against COVID-19 hospitalisations stratified by specific populations of interest (e.g., age groups, underlying chronic conditions, COVID-19 risk factors, immunocompromised), after adjusting for potential confounders • Estimate the effectiveness against COVID-19 hospitalisations stratified by SARS-CoV-2 variants to the extent such data are available	COVID-19 vaccine effectiveness in real-world setting	Protocol submission	30 April 2022
			Progress reports	31 January 2023, 31 July 2023, 31 January 2024, 31 July 2024
			Final report	31 January 2025
Study 2019nCoV-403 US Post-authorization Effectiveness Study Using a Claims and/or EHR Database Planned	• To assess the effectiveness of the Novavax COVID-19 vaccine in reducing clinically defined SARS-CoV-2 infection. • To assess the effectiveness of the Novavax COVID-19 vaccine in reducing clinically defined severe SARS-CoV-2 infection • To assess the effectiveness of a single dose of the Novavax COVID-19 vaccine in reducing clinically defined SARS-CoV-2 infection. • To assess the effectiveness of the Novavax COVID-19	COVID-19 vaccine effectiveness in real-world setting	Protocol submission	30 June 2022
			Progress reports	30 September 2023, 30 September 2024

Study/Status	Summary of objectives	Effectiveness uncertainties addressed	Milestones	Due dates
	vaccine against SARS-CoV-2 variants (where data are available) • To assess the effectiveness of the Novavax COVID-19 vaccine by subgroups e.g., age, sex, race/ethnicity, comorbidities/coinfections, prior SARS-CoV-2 infection, concomitant vaccinations, concomitant medications, and/or other characteristics.			

Overall conclusions on the Pharmacovigilance Plan

The proposed additional pharmacovigilance activities are appropriate for further characterisation the safety profile of the product and considering the pandemic circumstances.

2.7.3. Risk minimisation measures

Routine risk minimisation activities only are proposed to manage the safety concerns of the medicinal product.

Summary Table of Risk Minimisation Activities and Pharmacovigilance Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks: Not applicable		
Important potential risks		
Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)	Routine risk minimisation measures: None Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Specific adverse reaction follow-up questionnaire* Additional pharmacovigilance activities: **Ongoing clinical trials** • Study 2019nCoV-101 (Part 1); final CSR estimated date 31 March 2022. Study 2019nCoV-101 (Part 2); final CSR estimated date 31 December 2022

Safety concern	Risk minimisation measures	Pharmacovigilance activities
		• Study 2019nCoV-501; final CSR estimated date 31 December 2022 • Study 2019nCoV-302; final CSR estimated date 31 December 2022 • Study 2019nCoV-301; final CSR estimated date 30 September 2023 **Post-authorisation studies** • Study 2019nCoV-402 (Safety study using the UK CPRD database); final study report estimated date 30 June 2025 • Study 2019nCoV-404 (Safety study using a US-based claims and/or EHR database); final study report estimated date 30 September 2025
Anaphylaxis	Routine risk minimisation measures: SmPC sections 4.4 PL section 2 and section 4 Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Specific adverse reaction follow-up questionnaire* Additional pharmacovigilance activities: **Ongoing clinical trials** • Study 2019nCoV-101 (Part 1); final CSR estimated date 31 Mar 2022. Study 2019nCoV-101 (Part 2); final CSR estimated date 31 Dec 2022 • Study 2019nCoV-501; final CSR estimated date 31 Dec 2022 • Study 2019nCoV-302; final CSR estimated date 30 Sep 2022 • Study 2019nCoV-301; final CSR estimated date 30 Sep 2023 **Post-authorisation studies** • Study 2019nCoV-402 (Safety study using the UK CPRD database); final study report estimated date 30 June 2025 • Study 2019nCoV-404 (Safety study using a US-based claims and/or EHR database); final study report estimated date 30 September 2025
Myocarditis and pericarditis	Routine risk minimisation measures: None Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: **Ongoing clinical trials**

Safety concern	Risk minimisation measures	Pharmacovigilance activities
		• Study 2019nCoV-101 (Part 1); final CSR estimated date 31 March 2022. Study 2019nCoV-101 (Part 2); final CSR estimated date 31 December 2022 • Study 2019nCoV-501; final CSR estimated date 31 December 2022 • Study 2019nCoV-302; final CSR estimated date 31 December 2022 • Study 2019nCoV-301; final CSR estimated date 30 September 2023 **Post-authorisation studies** • Study 2019nCoV-402 (Safety study using the UK CPRD database); final study report estimated date 30 June 2025 • Study 2019nCoV-404 (Safety study using a US-based claims and/or EHR database); final study report estimated date 30 September 2025
Missing information		
Use in pregnancy and while breast feeding	Routine risk minimisation measures: SmPC Sections 4.6 and 5.3 PL Section 2 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: **Post-authorisation studies** • Study 2019nCoV-405 (Pregnancy and infant outcomes safety study using the "COVID-19 Vaccines International Pregnancy Exposure Registry" (C-VIPER)); final study report estimated date 30 June 2027
Use in immunocompromised patients	Routine risk minimisation measures: SmPC Section 4.4 PL section 2 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: **Ongoing clinical trials** • Study 2019nCoV-501; final CSR estimated date 31 December 2022 • Study 2019nCoV-302; final CSR estimated date 31 December 2022 • Study 2019nCoV-301; final CSR estimated date 30 September 2023 **Post-authorisation studies**

Safety concern	Risk minimisation measures	Pharmacovigilance activities
		• Study 2019nCoV-402 (Safety study using the UK CPRD database); final study report estimated date 30 June 2025 • Study 2019nCoV-404 (Safety study using a US-based claims and/or EHR database); final study report estimated date 30 September 2025
Use in frail patients with comorbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)	Routine risk minimisation measures: None Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond ADRs reporting and signal detection: None Additional pharmacovigilance activities: **Post-authorisation studies** • Study 2019nCoV-402 (Safety study using the UK CPRD database); final study report estimated date 30 June 2025 • Study 2019nCoV-404 (Safety study using a US-based claims and/or EHR database); final study report estimated date 30 September 2025
Use in patients with autoimmune or inflammatory disorders	Routine risk minimisation measures: PL section 2 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond ADRs reporting and signal detection: None Additional pharmacovigilance activities: **Post-authorisation studies** • Study 2019nCoV-402 (Safety study using the UK CPRD database); final study report estimated date 30 June 2025 • Study 2019nCoV-404 (Safety study using a US-based claims and/or EHR database); final study report estimated date 30 September 2025

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Interaction with other vaccines	Routine risk minimisation measures: SmPC Section 4.5 and 5.1 PL section 2 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond ADRs reporting and signal detection: None Additional pharmacovigilance activities: **Ongoing clinical trials** • Study 2019nCoV-302; final CSR estimated date 31 December 2022 **Post-authorisation studies** • Study 2019nCoV-402 (Safety study using the UK CPRD database); final study report estimated date 30 June 2025 • Study 2019nCoV-404 (Safety study using a US-based claims and/or EHR database); final study report estimated date 30 September 2025
Long term safety	Routine risk minimisation measures: None Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond ADR reporting and signal detection: None Additional pharmacovigilance activities: Ongoing clinical trials • Study 2019nCoV-101 (Part 1); final CSR estimated date 31 March 2022. Study 2019nCoV-101 (Part 2); final CSR estimated date 31 December 2022 • Study 2019nCoV-501; final CSR estimated date 31 December 2022 • Study 2019nCoV-302; final CSR estimated date 31 December 2022 • Study 2019nCoV-301; final CSR estimated date 30 September 2023 Post-authorisation studies • Study 2019nCoV-402 (Safety study using the UK CPRD database); final study report estimated date 30 June 2025 • Study 2019nCoV-404 (Safety study using a US-based claims and/or EHR database); final study report estimated date 30 September 2025

2.7.4. Conclusion

The CHMP and the PRAC considers that the risk management plan version 1 is acceptable.

Pharmacovigilance

2.7.5. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.7.6. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.8. New Active Substance

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

Information has been provided on the chemical formula, relative molecular mass, and structural formula/ amino acid sequence of the SARS-CoV-2 rS protein.

Keyword and sequence searches were conducted in established databases and no relevant patent literature was identified that describes the SARS-CoV-2 recombinant spike protein. Details about the searches performed are provided, using keyword-based searches and sequence-based searches.

The applicant has provided sufficient evidence that the quality aspects of NVX-CoV2373 are unique and that collectively, the information provided support the claim that the SARS-CoV-2 recombinant spike protein included as active substance in Nuvaxovid can be considered as a New Active Substance in itself.

In conclusion, the active substance NVX-CoV2373, i.e. the protein product of a recombinant SARS-CoV-2 S-gene encoding the 1260 (full length 1273 amino acid protein minus the signal peptide) amino acid spike protein, contained in the medicinal product Nuvaxovid can be considered a biological substance not previously authorised in a medicinal product in the European Union, i.e. it is considered a New Active Substance in itself.

2.9. Product information

2.9.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable, given the current urgent public health need for rapid development and approval of vaccines to prevent the global burden of disease associated with SARS-CoV-2 infection and COVID-19 disease, and because the product will

always be administered by a healthcare professional.

The applicant is expected to thoroughly review and update the package leaflet in the light of the results from the user testing, especially as regards the section 'Information about storage and handling'.

2.9.2. Labelling exemptions

The following exemptions from labelling requirements have been granted on the basis of article 63.3 of Directive 2001/83/EC. In addition, the derogations granted should be seen in the context of the labelling flexibilities described in the Questions and Answers on labelling flexibilities for COVID-19 vaccines (EMA/689080/2020 rev.3) document which aims at facilitating the preparedness work of COVID-19 vaccine developers and the associated logistics of early printing packaging activities.

Outer and immediate packaging in EN only:

Outer and immediate labelling will be provided in English only for all EU Member States (MSs), as well as Norway and Iceland. The labelling flexibility is granted until end of June 2022.

EN only printed package leaflet:

If required, EN printed package leaflet (PL) will be supplied to EU MSs, including Norway and Iceland. Except for those countries that require it in their national language as per labelling Q&A. The applicant plans to provide electronic and downloadable national translations of the Package Leaflet for other Member States / languages via a QR code. The labelling flexibility is granted until end of June 2022.

Omission of the Blue Box information on the outer carton:

Due to the use of one unified EN packing across all the EU countries, the Blue Box will not be displayed on the outer carton. The labelling flexibility is granted until end of June 2022.

The information, normally provided in the market specific packaging Blue Box area of the carton, will be provided as an electronic version on the website (via the QR code/URL).

Exemption from the obligation of serialisation:

All EU Member States have accepted a temporary derogation from serialisation for a period of 3 months starting from the EC decision date and only for supplies from the Serum Institute of India (SIIPL).

All other approved manufacturing sites will supply serialised packs as of launch date.

For the Serum Institute of India derogation, the MAH shall provide a progress report by end of February 2022 referring to details on the progress achieved in terms of ensuring serialisation compliance.

The MAH shall adhere to all the additional mitigating measures as stated in their exemption request letter.

The MAH will liaise with national stakeholders to inform them in advance which batches will and will not be serialised.

2.9.3. Quick Response (QR) code

A request to include a QR code in the labelling and the package leaflet for the purpose of providing information to Healthcare Professionals and vaccine recipients has been submitted by the applicant and has been found acceptable by all EU MSs, including Norway and Iceland.

The following elements have been agreed to be provided through a QR code:

Statutory information:

- Approved regulatory information, including the patient information leaflet (PIL) and Summary of Product Characteristics (SmPC);
- Vaccination Card.

2.9.4. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Nuvaxovid (COVID-19 Vaccine (recombinant, adjuvanted)) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU and it is approved under a conditional marketing authorisation.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The claimed indication for Nuvaxovid is active immunisation of individuals ≥18 years of age for prevention of coronavirus disease 2019 (COVID-19). COVID-19 is a respiratory disease caused by the novel coronavirus SARS-CoV-2. The virus has spread world-wide during 2020 causing WHO to declare a pandemic in March 2020. The virus infects the airways and causes a broad spectrum of respiratory symptoms ranging from asymptomatic infection to Severe Acute Respiratory Syndrome (SARS) and ARDS. The pandemic is still ongoing despite unprecedented efforts to control the outbreak.

3.1.2. Available therapies and unmet medical need

At the time of authorisation of this vaccine, five medicinal products had received marketing authorisation for the treatment of COVID-19. These encompass antiviral therapy (remdesivir), anti-inflammatory therapy (dexamethasone), IL-6 inhibitor (toculizumab) as well as monoclonal antibodies directed against the spike protein (casirivimab / imdevimab, regdanvimab and sotrovimab). Further, marketing authorisation applications were submitted for anakinra, baricitinib (both anti-inflammatory agents), as well as the direct acting antiviral drug molnupiravir. A rolling review was ongoing for tixagevimab / cilgavimab. Other widely used treatments for hospitalised patients include anticoagulants. These therapies have shown variable efficacy depending on the severity and duration of illness.

While care for individuals with COVID-19 has improved with clinical experience gained over time, there remains an unmet need worldwide for vaccines able to prevent or mitigate COVID-19 during the ongoing pandemic.

There are currently four COVID-19 vaccines authorised in the EU to prevent COVID-19. A high global demand for suitable vaccines to help counteract the ongoing pandemic remains.

3.1.3. Main clinical studies

The main evidence for efficacy for Nuvaxovid is based on two pivotal observer blinded, randomised, placebo controlled trials conducted in the US, Mexico (2019nCoV-301) and the United Kingdom (2019nCoV-302). The trials were designed to demonstrate efficacy against PCR-confirmed symptomatic coronavirus disease 2019 (COVID-19) diagnosed ≥ 7 days after completion of the second study vaccination (given 21 days after the first dose) in adult participants serologically negative (to SARS-CoV-2) at baseline until the endpoint-driven efficacy analysis was triggered by the occurrence of a prespecified number of blinded endpoints.

In study -302, 15,187 subjects were randomised 1:1 to receive NVX-CoV2373 or placebo (saline). In study -301, 29,949 subjects were randomised 2:1 to NVX-CoV2373 or placebo. The primary efficacy analyses were conducted in 14,039 (92.4%) randomised participants in 2019nCoV-302 and 25,452 (85.0%) randomised participants in 2019nCoV-301. The efficacy analysis was event-driven in both studies, with 62 cases in the interim and 106 in the final analysis for 2019nCoV-302, and 77 cases for the analysis in 2019nCoV-301.

3.2. Favourable effects

The estimated VE for the single primary analysis based on 77 accrued cases in 2019nCoV-301 was 90.4% (95% CI: 82.9, 94.6). Vaccine efficacy according to the primary efficacy endpoint was therefore demonstrated for both pivotal trials. The confirmatory analysis at the interim analysis based on 62 accrued cases in 2019nCoV-302 indicated a VE point estimate of 89.3% with a multiplicity adjusted 96.9% CI of 73.0% to 95.8%, meeting the prespecified study success criterion of an alpha-adjusted LBCI > 30%. VE was consistent in the final efficacy analysis after accrual of 106 cases, with an estimated VE of 89.7% (95%CI: 80.2, 94.6%).

In 2019nCoV-301, 4 cases were classified as severe, all in the placebo group. With respect to hospitalisation, there was 1 case of COVID-19 hospitalisation in 2019nCoV-302 and 3 in 2019nCoV-301. At the time of the final analysis in 2019nCoV-302 there were 4 cases classified as severe in the placebo group and none in the NVX-CoV2373 group occurring at least 7 days after the second dose in serologically negative adult participants in the PP-EFF analysis set.

The efficacy was consistent with the level of protection in the general study population in older adults ≥65 years [2019nCoV-302: estimated VE 88.9% [95% CI: 20.2; 99.7] based on 1/1953 vs 9/1957 cases for vaccine and control groups respectively], and in participants with comorbid conditions [2019nCoV-302: estimated VE 90.9% [95% CI: 70.4; 97.2]; based on 3/3117 vs 33/3143 cases for vaccine and control groups respectively; 2019nCoV-301: estimated VE 90.8% [95% CI: 79.2; 95.9]; based on 7/8109 vs 34/3910 cases].

The estimated VE of NVX-CoV2373 to prevent symptomatic mild, moderate, or severe COVID-19 due to a SARS-CoV-2 variant considered a VOC or VOI in baseline seronegative adult participants in 2019nCoV-301 was 93.2% (95% CI: 84.0, 97.1). The most common VOC was B.1.1.7 (Alpha), which was found in 46 cases. 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 in 2019nCoV-302 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.

An immune response in terms of both the humoral response against S protein (binding antibodies) and SARS-CoV-2 virus (neutralisation assays) and the cellular response have been shown in vaccinated subjects. The second dose is required to improve immunogenicity. Furthermore, safety and immunogenicity data from 2019nCoV-101 supported the inclusion of the adjuvant.

3.3. Uncertainties and limitations about favourable effects

Data on vaccine efficacy is available for 76 days for study 2019nCoV-301 and approximately 90 days since dose 2 from 2019nCoV-302. Therefore, the duration of protection is unknown. Longer-term vaccine efficacy will be further followed post-authorisation.

Although encouraging trends were observed, reliable efficacy estimates against severe COVID-19 and hospitalisation caused by COVID-19 could not be established due to the lack of a sufficient number of cases within the clinical studies. From the experience with other vaccines it is expected that prevention of severe COVID-19 will be achieved by preventing COVID-19 overall.

Although observed point estimates of vaccine efficacy were consistent across age groups, the number of cases in 65 to 84 years of age were limited.

Available data are insufficient to establish efficacy in subjects seropositive for SARS-CoV-2 at baseline. However, efficacy is anticipated in this group to the extent that natural immunity does not fully protect against re-infection, which is presently not fully characterised.

Immunocompromised patients were excluded from the trials, as well as pregnant and breast-feeding women. Few HIV+ subjects were enrolled in the supportive trial 2019nCoV-501. Further data in these subgroups should be collected post-authorisation. Data are limited in subjects with severe and/or uncontrolled underlying disease, and there is no data in persons with autoimmune diseases since these subjects were excluded from the clinical trials.

Although efficacy was shown against the B.1.1.7 variant, strain specific efficacy results should be interpreted with caution given the low number of cases for individual strains and potential confounding. The extent of cross-neutralisation of circulating and newly emerging strains of SARS-CoV-2 (including Delta and Omicron) remains uncertain, more data should be generated post-authorisation.

Further support for the efficacy of NVX-CoV2373 comes from trial 2019nCoV-501 which was conducted in South Africa and included both HIV-negative and HIV-positive participants. During the trial, a new variant emerged (B.1.351, Beta variant). The overall estimated VE in this study (48.6% (95% CI: 28.4, 63.1)) is lower than what is observed in study 2019nCoV-301 and 2019nCoV-302, also when looking only at the HIV-negative population. Whilst this may to some extent be explained by the circulating variant (Beta), immunogenicity results of the participants enrolled in this study also point to a reduced immune response after vaccination (measured against the Wuhan strain) compared to the response observed in 2019nCoV-302. Thus, it cannot be excluded that the lower VE is explained by more factors than the circulating virus variant alone, for example differences in baseline characteristics of the population enrolled, or potential batch related issues.

To date no correlate of protection has been established. Therefore, the clinical relevance of immunogenicity data is difficult to interpret.

3.4. Unfavourable effects

The safety was characterised in four clinical trials, in which 30,058 participants have been exposed to NVX-CoV2373 of whom 28,963 (96.4%) to two doses. The placebo group included 19,892 participants, with 19,270 (96.9%) receiving two doses. The median duration of follow-up in the pooled safety database was 70 days post-Dose 2.

Solicited local and systemic reactions were reported at a higher incidence in the NVX-CoV2373 group than in the placebo group after each injection. The frequency and severity of solicited reactions increased with the second dose compared to the first.

In 2019nCoV-302/2019nCoV-301, *solicited local AEs* were reported by 58% of NVX-CoV2373 recipients following the first dose and 79% following the second dose, compared to 21% and 21% of placebo recipients after the first and second dose respectively. Pain and tenderness were the most commonly reported local reactions in both pivotal studies, reported by 34% (pain) and 53% (tenderness) after the first dose of NVX-CoV2373. After the second dose, pain was reported by 59% and tenderness by 74%. In the placebo group rates were between 11% and 17% and did not increase with the second dose. Local reactions were mostly mild to moderate, with 1.1% of participants in the NVX-CoV2373 group reporting grade 3 local reactions after the first dose in either study and 6.6% after the second dose. Local reactions pain and tenderness had a median duration of 1 to 2 days after the first dose and 2 to 3 days after the second dose.

Headache, fatigue, and muscle pain were the most frequent *solicited systemic AEs*, reported by 25%, 25%, and 23% post dose 1 compared to 23%, 22%, and 13% in the placebo group respectively, and by 44%, 49%, and 48% post dose 2 compared to 19%, 21%, and 12% in the placebo group. The median duration of headache, fatigue and muscle pain was 1 day after each dose in both studies. For GI reactions (nausea/ vomiting), after the first dose rates are comparable between the NVX-CoV2373 group and the placebo group, however with the second dose reported nausea/vomiting doubled in the vaccine group. The median duration of headache, fatigue and muscle pain was 1 day after each dose. Fever increased substantially with the second dose in the NVX-CoV2373 group (from 0.5% after dose 1 to 5.6% after dose 2).

Systemic reactions were mostly mild with 2.3% reporting grade 3 systemic reactions after the first dose, and 12% reporting grade 3 systemic reactions following the second dose. Grade 4 reactions were reported by 0.1%.

In the safety subsets, unsolicited AEs within the 49 days after first vaccination (28 days after the second dose) were reported more frequently in NVX-CoV2373 recipients than among placebo recipients overall (23.8% vs 18.7% in study 2019nCoV-302 and 16.3% vs 14.8% in 2019nCoV-301). This was driven mainly by the SOC of general disorders and administration site conditions, nervous system disorders and musculoskeletal and connective tissue disorders, which mostly reflect the reactogenicity of NVX-CoV2373. A similar imbalance was seen in treatment-related TEAEs, which again was explained by the reactogenicity. Severe TEAEs occurred in < 1% of participants.

A numerical imbalance was seen in the reports of severe TEAEs related to hypertension in 2019-nCoV302. In a pooled safety analysis, a higher incidence of hypertension following NVX-CoV2373 was seen in older adults, over 65 years of age. There were 4 SAEs of hypertension as well as 13 severe cases of hypertension in the NVX-CoV2373 vaccinated participants. Hypertension is considered an adverse drug reaction of NVX-CoV2373.

There were no deaths considered related to study vaccine, with similar rates between vaccine groups.

Overall, the incidence of SAEs was low and similar in the between the vaccine groups in study 2019nCoV-302 and 2019nCoV-501. In study 2019nCoV-301, there were numerically more SAEs in the

SOC of Hepatobiliary Disorders, mainly driven by events related to cholecystitis (9 vs 0). Additionally, there were more serious adverse events of prostate cancer (5 vs 0), cerebrovascular accident (7 vs 1) and hypertension/hypertensive crisis (4 vs 0) in the NVX-CoV2373 treatment group.

There were three cases of myocarditis following vaccination with NVX-CoV2373, which may be related to the vaccine based on the TTO. Considering the experience with other COVID-19 vaccines, myocarditis was included as an important potential risk in the RMP.

3.5. Uncertainties and limitations about unfavourable effects

There is a lack of long-term safety data, with a median follow up of 3 months after the second dose in the pivotal trials. Long term safety up to 1 year is available for the platform (Recombinant Nanoparticle Vaccine Antigens with Matrix-M1 Adjuvant) with no emerging safety signal.

No difference was observed with regard to the incidence and severity of reactogenicity in subjects who were seropositive for SARS-CoV-2 at baseline compared with subjects who were seronegative for SARS-CoV-2 at baseline.

Whilst hypertension has been identified as an uncommon adverse drug reaction for Nuvaxovid, there is insufficient information available to determine the clinical impact of this ADR.

Immunosuppressed /immune-deficient individuals, with exception of HIV infected individuals on stable antiviral therapy, were excluded from the study. The safety database for immunocompromised individuals is limited to 244 subjects with medically stable HIV infection (122 in each treatment group) included in 2019nCoV-501. The submitted safety and reactogenicity data in this subpopulation did not reveal any concern. No safety data are available for immunocompromised individuals other than HIV. No safety data are available for individuals with autoimmune disorders and individual under immune-suppressive treatment.

There is limited clinical data in pregnant women, with 95 pregnancies reported in the clinical trials of which the majority (60) were still ongoing at the time of reporting. There were no stillbirths or foetal deaths. There are no data available on the safety of Nuvaxovid administered during breastfeeding.

Persons with stable comorbidities were included in the pivotal trials. In 2019nCoV-302, almost half of participants (45%) had a comorbidity or BMI greater than 30. In 2019nCoV-301, the majority of participants were overweight or obese (70.2%), 14% had a chronic lung disease, 8% had Diabetes mellitus type 2, 1% had cardiovascular disease and 0.6% had chronic kidney disease. There were lower frequencies and intensities of solicited local and systemic AEs after each vaccination among Nuvaxovid recipients with co-morbidities of obesity, chronic kidney disease, cardiovascular disease, and diabetes mellitus type 2 than the overall population. Frailty has not been evaluated yet. Therefore, use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease COPD, diabetes, chronic neurological disease, cardiovascular disorders) has been identified as missing information in the safety specifications of the RMP.

Available non-clinical and clinical data do not raise a concern regarding vaccine-enhanced respiratory disease. The possibility of enhanced disease cannot be excluded with certainty and is listed as an important potential risk in the RMP.

3.6. Effects Table

Table 39 Effects Table for NVX-CoV2373 in the prevention of COVID-19 in adults <(data cut-off: 23-02-2021 (2019nCoV-302), 01-06-2021 (2019nCoV-301)>

Effect	Short Description	Unit	NVX-CoV2373	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Vaccine efficacy overall – study -302	Prevention of symptomatic mild, moderate, or severe COVID-19 with onset from at least 7 days after second vaccination in baseline seronegative (to SARS-CoV-2) adult participants	VE % (95% CI)	89.7% (80.2, 94.6%)		SoE: Robust data showing vaccine efficacy after 7 days post second dose, further supported by the different secondary endpoints SoE: Efficacy observed in the elderly (≥65yoa) SoE: Efficacy observed in participants with comorbidities Unc: Short median follow up of 90 and 76 days	Study 2019nCoV-302
		n cases/n subjects at risk for the endpoint	10/7020	96/7019		
Vaccine efficacy overall – study -301		VE % (95% CI)	90.4% (82.9, 94.6%)			Study 2019nCoV-301
		n cases/n subjects at risk for the endpoint	14/17312	63/8140		

Unfavourable Effects						
Headache	Solicited systemic AEs	% of individuals reporting the ADRs	50%	31%	Transient effect, majority mild to moderate in severity ADRs milder and reported much less frequently in older adults (≥ 65 years old).	Pooled data from Study 2019nCoV-301 and Study 2019nCoV-302
Fatigue			53%	31%		
Muscle pain			51%	19%		
Injection site pain	Solicited local AEs		62%	19%		Pooled data from Study 2019nCoV-301 and Study 2019nCoV-302
Injection site tenderness			75%	24%		

Abbreviations: ADR: Adverse Drug Reaction, AE: Adverse Event, CI: Confidence Interval, SoE: Strength of Evidence, VE: Vaccine Efficacy, UnC: Uncertainty

Notes: only the most frequently reported adverse reactions are listed. For a full summary of all adverse reactions refer to the Summary of Product Information section 4.8

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Overall, vaccine efficacy of two doses of Nuvaxovid administered with an interval of 21 days has been demonstrated for the prevention of symptomatic COVID-19 disease with onset of at least 7 days after second vaccination in adults ≥18 years of age, as well as an acceptable safety profile, based on two large pivotal phase 3 trials included in this cMAA.

The results are considered robust based on the study design and are further supported by the different secondary endpoints and analyses.

Subgroup analyses of the primary efficacy endpoint showed efficacy for elderly (≥65 years), as well as for participants with medical comorbidities associated with high risk of severe COVID-19, which is considered as the population at highest need for preventative strategies.

Efficacy against COVID-19 was demonstrated in each participating country, including South Africa (where the variant of concern B.1.351 (Beta) was the predominant circulating strain during the study), although efficacy was of lower magnitude compared to other region/countries.

No reliable efficacy estimate can currently be established against severe COVID-19 or hospitalisation; however, it is likely that severe disease will be prevented as a consequence of preventing symptomatic COVID-19. Further follow up is expected in post-authorisation effectiveness studies to confirm this.

A shortcoming of the current efficacy dataset is the short median follow up of approx. 90 days since dose 2 from 2019nCoV-302 and 76 days for 2019nCoV-301. Longer-term vaccine efficacy will be further followed post-authorisation.

It would be desirable to confirm if this vaccine also has an effect on asymptomatic infection and viral transmission. This is evaluated as part of secondary objectives in both pivotal trials and data are expected post-authorisation. These aspects however may not be adequately characterised based on clinical trial data and will likely need to be further elucidated post-authorisation.

The observed safety profile is considered well characterised and acceptable based on the short-term data available. The safety of Nuvaxovid is mainly characterised by local and systemic reactions occurring during the first 7 days after vaccination. Reactions were mostly mild to moderate, transient and self-limited. Reactions were more frequent and more severe with the second dose. The reactogenicity was milder and lower in older adults aged ≥65 years compared to the younger adults aged ≥18 to 64. SAEs and AESIs were infrequent in the NVX-CoV2373 and placebo groups.

Long term safety has to be characterised further, and it is important to analyse the full safety follow-up of the ongoing trials, which is 12 months for 2019nCoV302 and 2019nCoV501, and 24 months for 2019nCoV301 The current dataset gives no indication of vaccine-enhanced disease, a potential risk that will be followed up as detailed in the RMP.

There is limited data on use in pregnant women, but a protective effect is anticipated. Preclinical data are reassuring; therefore, noting that pregnancy as such is a risk factor for severe COVID19, and that pregnant women may additionally belong to other risk groups, vaccination may be considered on a case by case basis. Data in pregnancy will be generated post-authorisation. There are no data in breast-feeding women. Based on biological plausibility, no risk in breast-feeding is anticipated.

No participants with severe immunodeficiency were included in the studies. Such patients may not be protected as well as immunocompetent individuals by vaccination. However, no safety issues are anticipated, and the benefit-risk balance in immunocompromised subjects is deemed positive, also in light of the underlying excess risk of COVID-19. Further data should be collected post-authorisation. Also, subjects with severe underlying diseases were not included in the studies, and the safety and effectiveness of the vaccine in these groups will be followed up post-authorisation.

Regarding seropositive subjects, no safety issues have been observed in this population, and efficacy can be anticipated. Therefore, the vaccine can be administered without performing previous SARS-CoV-2 serology testing.

Uncertainties concerning the pharmaceutical characterisation of the commercial product are compatible with a positive benefit-risk balance.

3.7.2. Balance of benefits and risks

The available clinical data for Nuvaxovid, including the induction of immune responses and the demonstrated vaccine efficacy, establish the benefits to prevent COVID-19 in immunised individuals 18 years of age and older. The lack of any serious safety concerns for subjects aged 18 years and above allows concluding on a positive benefit-risk balance in the proposed indication.

3.7.3. Additional considerations on the benefit-risk balance

Given the current pandemic situation, the demonstrated favourable effect and considering the overall characteristics of the unfavourable effects, a positive benefit-risk balance in the proposed indication is concluded for this vaccine.

Conditional marketing authorisation

The potency of the finished product batches used in clinical studies was not adequately linked to the potency of the commercially manufactured batches, raising uncertainty in comparing the potency of commercial finished product batches with those of clinical batches and defining clinically qualified potency limits based on batches used in clinical phase 3 trials. Based on the clarifications provided by the applicant, it can be concluded that the commercial batches are at least as potent as the least potent batch used in clinical studies. In addition, the lower limit for the product potency specification was increased, which is considered a conservative approach. However, to further support this conclusion, as a Specific Obligation, the applicant should bridge the relevant reference standard lots (i.e. calibrate reference standards BN2-0620-047 and 20_PRS_SARS-CoV-2 against each other in the Gen1v2 finished product assay in the presence of Matrix-M1) to firmly link the potencies of finished product batches used in clinical phase 3 studies to those of commercial batches. Once the reference standards are adequately bridged, the finished product release and shelf-life acceptance criteria of the potency assay should be reviewed and updated as appropriate.

The proposed specifications, as demonstrated by the submitted data, are suitable to control product quality. Due to the development of this vaccine under accelerated timelines, real time stability data for finished product are limited. However, data from clinical batches are considered representative to support the shelf life of the finished product. As a Specific Obligation the applicant is requested to provide additional stability data on commercial batches to further support the shelf life of the product.

The characterisation and control of the active substance and finished product are considered acceptable in the context of a conditional Marketing Authorisation in the current (COVID-19) pandemic emergency situation. Nevertheless, additional data to ensure consistent quality are considered important to confirm the finished product stability and to ensure appropriate links to the clinical material in relation to control of potency, and these data should be provided post-authorisation as specific obligations to the MA.

Studies are underway and it is expected that the applicant will be able to provide the requested data and thereby fulfil the specific obligations. Based on the applicant's justification and commitment, it is expected that data to fulfil the specific obligations will be submitted between February 2022 and end of January 2023.

As comprehensive data on the product are not available, a conditional marketing authorisation was requested by the applicant in the initial submission.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the prevention of a life-threatening disease. Furthermore, the CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive, as discussed.
- It is likely that the applicant will be able to provide comprehensive data.

Nuvaxovid falls within the scope of the conditional marketing authorisation Article 3(1) of Regulation (EC) No 726/2004 indent 2: Medicinal products to be used in emergency situations as recognised by Decision of the European Parliament and of the Council No. 1082/2013/EU on serious cross-border

threats to health amended with date of last review on 28/05/2020 to adopt measure to cope with the impact of the crisis following the COVID-19 outbreak. For Module 3 data the commitments are made with specified timelines and data will be delivered accordingly. It is therefore considered likely that the applicant will be able to provide the requested data and thereby fulfil the specific obligations.

- Unmet medical needs will be addressed.

Currently, four COVID-19 vaccines are authorised in the EU, under conditional marketing authorisations: Comirnaty, Spikevax, Covid-19 Vaccine Janssen, and Vaxzevria. While these vaccines all demonstrated a positive benefit-risk balance, they are not covering the supply need in the European Union, and there is still an urgent need to provide additional prophylactic options in the context of the pandemic across the EU. Further authorised vaccines are therefore needed to increase the total supply and availability to fully vaccinate the EU/EAA population.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

The product provides immediate benefit for the vaccinated population in preventing COVID-19 disease. Data from Israel are suggesting that vaccination not only prevents COVID-19, but also limits the spread of the virus. Decreasing the number of patients suffering from COVID-19, as well as the spread of the virus impacts positively the health care systems, not only financially, but primarily in terms of capacity and focus on standard care of other diseases. Moreover, data from clinical trials also show Nuvaxovid protection from new variant strains (e.g., B.1.1.7/501Y.V1 first identified in the UK and B.1.351/501Y.V2 first identified in South Africa). According to the WHO´s COVID-19 Strategic Preparedness and Response Plan for 2021, vaccine availability, accessibility, and deployment are the highest health, social, economic, and political priorities for virtually every country, agency, business and community around the world.

The justifications presented by the applicant are considered valid and acceptable. Therefore, a Conditional marketing authorisation may be granted as long as the benefit-risk balance of Nuvaxovid remains positive after the assessment of all submitted data.

3.8. Conclusions

The overall benefit-risk balance of Nuvaxovid is positive, subject to the conditions stated in section 'Recommendations'.

Eligibility to a conditional marketing authorisation as well as requirements have been demonstrated in line with provisions of Article 14-a of Regulation (EC) No 726/2004.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Nuvaxovid is favourable in the following indication:

Nuvaxovid is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

The CHMP therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

In view of the declared Public Health Emergency of International Concern and in order to ensure early supply this medicinal product is subject to a time-limited exemption allowing reliance on batch control testing conducted in the registered site(s) that are located in a third country. This exemption ceases to be valid on 31 March 2022. Implementation of EU based batch control arrangements, including the necessary variations to the terms of the marketing authorisation, has to be completed by 31 March 2022 at the latest.

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Official batch release

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

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

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

An updated RMP should be submitted:

At the request of the European Medicines Agency;

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

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

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

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that SARS-CoV-2 recombinant spike protein is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Refer to Appendix on new active substance (NAS).

Annex I – List of Recommendations

Area	Number	Description	Classification*	Due date
Quality, 3.S.2.2. Description of Manufacturing Process and Process Controls	1	The MAH is recommended to explore possibilities to further optimise the manufacturing process with regard to removal of impurities.	REC	Updates on an annual basis, starting 31 Dec 2022
Quality, 3.2.S.2.3 Control of Materials	2	The MAH is recommended to submit the results of the ongoing characterisation of baculovirus seed virus by *in vitro, in vivo* and *in ovo* adventitious agents tests.	REC	31 Jan 2022
Quality, 3.2.S.2.3 Control of Materials	3	The MAH is recommended to develop an updated Risk Assessment that will represent all studies, justifications and technical considerations for the use of Next Generation Sequencing, and to ensure that it reflects the current control strategy and viral clearance study results. This evaluation should also include comparison of the *in vitro* pharmacopeial method and the NGS test method.	REC	31 Mar 2022
Quality, 3.2.S.2.3 Control of Materials	4	The MAH is recommended to determine the sequence for the PVS (Pre-Master Virus Stock), Master Virus Stock, Working Virus Stock, and the virus in the culture harvest collected from the production bioreactor, and send the report and Certificates of Analysis, as available.	REC	01 March 2022
Quality, 3.2.S.2.3 Control of Materials	5	The MAH is recommended to provide a stability testing plan for the Master Virus Stock and Working Virus Stock.	REC	01 March 2022
Quality, 3.2.S.2.5 Process validation	6	The MAH is recommended to provide the results from the outstanding spiroplasma test.	REC	31 Jan 2022
Quality, 3.2.S.2.5 Process validation	7	The MAH is recommended to provide the updated active substance PPQ summary report, including the PPQ host cell protein data.	REC	01 Feb 2022
Quality, 3.2.S.2.5 Process validation	8	The MAH is recommended to provide protocols for the at-scale resin lifetime.	REC	01 Feb 2022
Quality,	9	The MAH is recommended to submit the data from the thermal stress studies in	REC	31 Jan 2022

Area	Number	Description	Classification*	Due date
3.2.S.2.6 Manufacturing Process Development		support of the comparability between FDBU and SIIPL active substance lots.		
Quality, 3.2.S.3 Characterisation	10	The MAH is recommended to screen the most abundant HCP / HVP present at > 0.5% of total protein for an overlap in epitopes with human proteins.	REC	30 Jun 2022
Quality, 3.2.S.3 Characterisation	11	The MAH is recommended to continue to investigate additional parameters for peptide mapping MS to cover a long hydrophobic domain near the C-terminus.	REC	30 Jun 2022
Quality, 3.2.S.3 Characterisation	12	The MAH is recommended to characterise the glycosylation profile for the next 10 batches manufactured at SIIPL. Based on the data the MAH should present an evaluation on the need for any further monitoring or control of the glycosylation profile.	REC	30 Jun 2022
Quality, 3.2.S.3 Characterisation	13	The MAH is recommended to develop a method to confirm the expected disulfide bonds.	REC	30 Jun 2022
Quality, 3.2.S.3 Characterisation	14	The MAH is recommended to develop a CE-SDS method and provide identification of the peaks in the final electropherogram. A discussion of the data and final confirmation of the molecular weights should be provided. Further, the MAH is recommended to, upon completion of successful method development and validation of the CE-SDS method, to implement justified acceptance criteria for active substance and finished product release and stability testing.	REC	31 Dec 2022
Quality, 3.2.S.3 Characterisation	15	The MAH is recommended to develop a HPSEC-MALS method intended to provide a qualitative assessment of the various structures present in the active substance.	REC	30 Jun 2022
Quality, 3.2.S.3 Characterisation	16	The MAH is recommended to develop a MS method to confirm MW of intact rS.	REC	31 March 2022
Quality,	17	The MAH is recommended to develop an HCP ELISA assay to better control HCP	REC	30 Jun 2022

Area	Number	Description	Classification*	Due date
3.2.S.4 Control of drug substance		impurities in the active substance. Once a suitable assay is qualified, it should be implemented to demonstrate in-process HCP clearance.		
Quality, 3.2.S.4 Control of Drug Substance	18	The MAH is recommended to validate and implement the improved Mass Spectrometry (MS) method to quantitate the levels of rS and seven predominant HCPs in active substance lots. It is recommended to set specifications after testing 10 active substance lots.	REC	31 March 2022
Quality, 3.2.S.4 Control of drug substance	19	The MAH is recommended to perform a spiking study with the SDS-PAGE method to demonstrate the quantitative capability of the method.	REC	30 Jan 2022
Quality, 3.2.S.4 Control of drug substance	20	The MAH is recommended to submit the validation report for the adventitious agents test with the C6/36 cell line.	REC	31 Dec 2021
Quality, 3.2.S.4 Control of drug substance	21	The MAH is recommended to complete the endotoxin hold time study to ensure that the samples do not exhibit masking and impact low endotoxin recovery.	REC	30 Jun 2022
Quality, 3.2.S.4 Control of drug substance	22	The MAH is recommended to provide a comparison between Mass Spectrometry and SDS-PAGE data for both FDBU and SIIPL active substance lots.	REC	15 Feb 2022
Quality, 3.2.S.4 Control of drug substance & 3.2.P.5 Control of Finished product	23	The MAH is recommended to re-evaluate the active substance and finished product total protein specification limits after the statistical analysis of 30 commercial scale lots and to provide this re-evaluation once available.	REC	30 Jun 2022
Quality, 3.2.S.7 Stability	24	The MAH is recommended to implement a shelf-life specification for purity of active substance using SDS-PAGE.	REC	30 Jun 2022
Quality, 3.2.S.7 Stability	25	The MAH is recommended to provide additional stability data for active substance samples stored under long-term and accelerated conditions.	REC	31 Jan 2022
Quality, 3.2.P.2 Pharmaceutical Development	26	The MAH is recommended to perform a shipping qualification study in order to evaluate the real-world impact of movement/ vibration/ agitation on the quality of the vaccine.	REC	31 Mar 2022

Area	Number	Description	Classification*	Due date
Quality, 3.2.P.2 Pharmaceutical Development	27	The MAH is recommended to provide results of the leachable study with the finished product in 5 ml specific vials with 13 mm rubber stoppers.	REC	30 Sep 2022
Quality, 3.2.P.2 Pharmaceutical Development	28	The MAH is recommended to provide data of a supporting short-term stability study that includes both polypropylene and polycarbonate syringes under various potential extended in-use environmental conditions.	REC	31 Jan 2022
Quality, 3.2.P.2 Pharmaceutical Development	29	The MAH is recommended to provide an updated analytical comparability report for finished product manufactured at PAR and SIIPL (report QAG_07396). This report should contain the TEM data on the smaller scale finished product lots, NTA data on the commercial scale finished product lots and the 3-month and 6-month thermal stress timepoints.	REC	31 Jan 2022 (updated report) 31 March 2022 (final report)
Quality, 3.2.P.3.5 Process Validation and/or Evaluation	30	The MAH is recommended to submit the full process validation report for the commercial scale finished product manufacturing process at the SIIPL Manjari premises once the results of the labelled lots (appearance, identity) are in place.	REC	31 Mar 2022
Quality, 3.2.P.3.5 Process Validation and/or Evaluation	31	The MAH is recommended to perform a bulk hold time study and to provide stability data for the intermediate hold time (NMT 24 hours).	REC	31 March 2022
Quality, 3.2.P.3.5 Process Validation and/or Evaluation	32	The MAH is recommended to provide a completed investigation of the increased endotoxin level in a finished product PPQ specified batch.	REC	31 Jan 2022
Quality, 3.2.P.5 Control of Finished product	33	The MAH is recommended to develop a purity test for finished product using SDS-PAGE and to establish a release and shelf life purity specification.	REC	30 Jun 2022
Quality, 3.2.P.5 Control of Finished product	34	The MAH is recommended to establish a two-sided specification for osmolality after a minimum of 30 finished product batches have been manufactured.	REC	22 Jun 2022

Area	Number	Description	Classification*	Due date
Quality, 3.2.P.5 Control of Finished product	35	The MAH is recommended to perform the container closure integrity test as described in the US Pharmacopoeia.	REC	30 Jun 2022
Quality, 3.2.P.5 Control of Finished product	36	The MAH is recommended to conduct further evaluation to confirm whether the upper limit of the finished product pH range is relevant for compatibility.	REC	31 March 2022
Quality, 3.2.P.5 Control of drug product	37	The MAH is recommended to submit the Validation report for the CBQCA method.	REC	7 January 2022
Quality, 3.2.S.4 Control of drug substance & 3.2.P.5 Control of Finished product	38	The MAH is recommended to include mean particle size and polydispersity index by dynamic light scattering in the active substance and finished product release and stability specification. In the meantime, particle size will be monitored for SIIPL with the current method version.	REC	30 Sep 2022
Quality, 3.2.P.8 Stability	39	The MAH is recommended to provide a separate stability protocol to describe the post-approval stability program for the finished product. This stability protocol should include stability limits for the characterisation tests and will be re-evaluated at the end of the study.	REC	30 Jun 2022
Quality, 3.2.P.8 Stability	40	The MAH is recommended to provide the full investigation report of the atypical low protein concentration results in the long term finished product stability studies for PAR lots 28003 and 28004.	REC	31 Jan 2022
Quality, 3.2.P.8 Stability	41	The MAH is recommended to update the statistical analysis of long term stability results as additional data becomes available for on-going stability studies for SIIPL and PAR finished product lots.	REC	31 March 2022
Quality, 3.2.A.3	42	The MAH is recommended to provide the results of the 2 years leachables study for the PETG bottle, when available.	REC	31 Jan 2022
Quality, 3.2.A.3	43	The MAH is recommended to provide the results of the verifying study of Matrix (-A or -C) in the Allegro 2D Biocontainers (bags), when available.	REC	30 Sep 2023 (2 year study); provide interim report annually

Area	Number	Description	Classification*	Due date
Quality, 3.2.A.3	44	The MAH is recommended to update the control specifications in 3.2.A.3.6 for the two proposed container closure systems for Matrix-A and Matrix-C (the Nalgene PETG Bottles and the Allegro 2D Biocontainer Bags) to further align with the Guideline on plastic immediate packaging materials.	REC	28 Feb 2022
Quality, 3.2.A.3	45	The MAH is recommended to revise the Matrix-A and Matrix-C specifications and to implement the same acceptance limits at release and shelf-life, unless justified.	REC	30 Jun 2022
Quality, 3.2.A.3	46	The MAH is recommended to review the shelf-life of Matrix-A and Matrix-C based on the updated specification and available stability data.	REC	30 Jun 2022
Non-clinical	47	In a study in Rhesus monkeys two doses (full human dose) of 5 µg SARS-CoV-2 rS with 50 µg Matrix-M1 adjuvant were well tolerated. The applicant should submit the final report to show the results on a challenge with the virus after 6 or 12 months as soon as available.	REC	As soon as available
Non-clinical	48	The applicant should conduct a biodistribution study in mice to evaluate the Matrix-M1 adjuvant and submit the results of this study as soon as available.	REC	As soon as available
Non-clinical	49	The applicant should submit immunogenicity data in baboons following boosting with updated immunogen based on South African virus variant as soon as available.	REC	As soon as available
Clinical	50	The applicant should investigate the need of a booster dose after primary series and submit these data as soon as available.	REC	As soon as available
Clinical	51	The applicant should detail their plans to establish an immunologic correlate of protection.	REC	As soon as available
Clinical	52	The applicant should investigate the ability of the vaccine to neutralise emerging SARS-CoV-2 variants and provide regular updates.	REC	As soon as available