

EU RISK MANAGEMENT PLAN

NUVAXOVID (COVID-19 VACCINE (RECOMBINANT, ADJUVANTED))

RMP version to be assessed as part of this application:

RMP version number: 3.1

Data lock point for this RMP: 22 December 2022

Date of final sign off: 06 February 2023

Rationale for submitting an updated RMP:

Type II variation to support homologous booster vaccination with Nuvaxovid in adolescent individuals 12-17 years of age.

Summary of significant changes in this RMP:

RMP Part/Module	RMP v3.1
PART I PRODUCT(S) OVERVIEW	Posology update to include booster dose in adolescents.
PART II SAFETY SPECIFICATION	
PART II Module SI Epidemiology of the Indication(s) and Target Populations	Update epidemiology information through data lock point (DLP) including booster dose in adolescents.
PART II Module SII Non-Clinical Part of the Safety Specification	No changes.
PART II Module SIII Clinical Trial Exposure	Update to include exposure data for adolescent and adult booster dose from study 2019nCoV-301.
PART II Module SIV Populations Not Studied in Clinical Trials	No changes.
PART II Module SV Post-Authorisation Experience	Update to reflect Nuvaxovid post-marketing exposure data.
PART II Module SVI Additional EU Requirements for the Safety Specification	No changes.
PART II Module SVII Identified and Potential Risks	Addition of safety data on adolescent and adult booster dose.
PART II Module SVIII Summary of Safety Concerns	No changes.
PART III PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)	
PART III.1 Routine Pharmacovigilance Activities PART III.2 Additional Pharmacovigilance Activities PART III.3 Summary Table of Additional Pharmacovigilance Activities	Update to study milestones of additional PV activities, as applicable.
PART IV PLANS FOR POST AUTHORISATION EFFICACY STUDIES	No changes.
PART V RISK MINIMISATION MEASURES (INCLUDING THE EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)	
PART V.1 Routine Risk Minimisation Measures PART V.2 Additional Risk Minimisation Measures PART V.3 Summary of Risk Minimisation Measures	No changes.
PART VI SUMMARY OF THE RISK MANAGEMENT PLAN	
I The medicine and what it is used for II Risks associated with the medicine and activities to minimise or further characterise the risks	Update to study/milestones as per Part III changes.

RMP Part/Module	RMP v3.1
PART VII ANNEXES TO THE RISK MANAGEMENT PLAN	
Annex 1 EudraVigilance interface	No changes.
Annex 2 Tabulated summary of planned, ongoing, and completed studies in the pharmacovigilance plan	Update to study milestones as per Part III changes.
Annex 3 Protocols for proposed, ongoing, and completed studies in the pharmacovigilance plan	No changes.
Annex 4 Specific adverse drug reaction follow-up forms.	No changes.
Annex 5 Protocols for proposed and ongoing studies in RMP Part IV	No changes.
Annex 6 Details of proposed additional risk minimisation measures (if applicable)	No changes.
Annex 7 Other supporting data (including referenced material)	Annex 7.A: Updated AESI List. Annex 7.B: Updated Vaccine Reminder Card example. Annex 7.C: Updated list of literature references.
Annex 8 Summary of changes to the risk management plan over time	Updated summary of changes to the RMP over time.

Other RMP versions under evaluation: None.

Details of the currently approved RMP:

Version number: 2.1

Approved with procedure: EMEA/H/C/005808/II/0028

Date of approval (opinion date): 01 December 2022

EU QPPV/QPPV Deputy name¹: Julia Appelskog

EU QPPV/QPPV Deputy signature: The content of this RMP has been reviewed and approved by Novavax's QPPV or QPPV Deputy (by delegation). The electronic signature is available on file.

¹ QPPV name will not be redacted in case of an access to documents request; see HMA/EMA Guidance document on the identification of commercially confidential information and personal data within the structure of the marketing-authorisation application; available on EMA website <http://ema.europa.eu>

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List of Abbreviations

Acronym	Abbreviation Definition
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
AFRO	African Region
AITD	Autoimmune Thyroid Disease
ARDS	Acute Respiratory Distress Syndrome
BMI	Body Mass Index
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease 2019
CPRD	Clinical Practice Research Datalink
CRP	C-Reactive Protein
CSR	Clinical Study Report(s)
CVE	COVID-19 Vaccine effectiveness
C-VIPER	COVID-19 Vaccines International Pregnancy Exposure Registry
DALY	Disability-adjusted Life Year
DLP	Data Lock Point
DM	Diabetes Mellitus
ECDC	European Centre for Disease Prevention and Control
EHR	Electronic Health Record
EMA	European Medicines Agency
EU	European Union
EUA	Emergency Use Authorisation
EEA	European Economic Area
EVDAS	EudraVigilance Data Analysis System
GLP	Good Laboratory Practice
GTIN	Global Trade Identification Number
HAART	Highly Active Antiretroviral Therapy
HCP	HealthCare Professional/Provider
HIV	Human Immunodeficiency Virus
HLT	High Level Term
ICSR	Individual Case Safety Report
ICU	Intensive Care Unit
IgE	Immunoglobulin E
IR	Incidence Ratio
IM	Intramuscular
IMD	Immune-Mediated Disease
IME	Important Medical Event
MedDRA	Medical Dictionary for Regulatory Activities

Acronym	Abbreviation Definition
MAAE	Medically Attended Adverse Event
MHC	Major Histocompatibility Complex
MIS-C	Multisystem Inflammatory Syndrome in Children
µg	Microgram(s)
mL	Milliliter(s)
NVX-CoV2373	Novavax Covid-19 Vaccine
O/E	Observed versus expected
PASS	Post-Authorisation Safety Study
PCR	Polymerase Chain Reaction
PIMMC	Potential Immune-Mediated Medical Conditions
PIMS-TS	Paediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2 infection
PRAC	Pharmacovigilance Risk Assessment Committee
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
PvSS	Pharmacovigilance Signaling System
rS	Recombinant spike
RIVM	National Institute for Public Health and the Environment
RMP	Risk Management Plan
RNA	Ribonucleic Acid
RSV	Respiratory Syncytial Virus
S	Spike
SAE	Serious Adverse Event
SARI	Severe Acute Respiratory Infection
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SCCS	Self-Controlled Case Series
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System Organ Class
SSR	Summary Safety Report(s)
SY	Subject Year(s)
TND	Test-Negative Design
TEAE	Treatment-Emergent Adverse Event
VAED	Vaccine-Associated Enhanced Disease
VAERD	Vaccine-Associated Enhanced Respiratory Disease
VAERS	Vaccine Adverse Event Reporting System
VOC	Variant of Concern
VOI	Variant of Interest

Part I: Product(s) Overview

Table Part I.1 Product(s) Overview

Active substance(s) (INN or common name)	COVID-19 Vaccine (recombinant, adjuvanted)
Pharmacotherapeutic group(s) (ATC Code)	Vaccine, other viral vaccines (J07BX03)
Marketing Authorisation Applicant	Novavax CZ a.s.
Medicinal products to which this RMP refers	1
Invented name(s) in the EEA	Nuvaxovid dispersion for injection
Marketing Authorisation procedure	Centralised
Brief description of the product	Chemical class Recombinant Protein Vaccine
	Summary of mode of action A 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 neutralizing antibodies, which may contribute to protection against COVID-19.
	Important information about its composition: One dose (0.5 milliliters (mL)) contains 5 micrograms (µg) of the SARS-CoV-2 spike protein (produced by recombinant DNA technology using Baculovirus expression system in an insect cell line that is derived from Sf9 cells of the <i>Spodoptera frugiperda</i> and is adjuvanted with Matrix-M. The adjuvant Matrix-M contains per 0.5 mL: Fraction-A (42.5 µg) and Fraction-C (7.5 µg) of <i>Quillaja saponaria</i> Molina extract.
Hyperlink to the Product Information	Nuvaxovid dispersion for injection Summary of Product Characteristics (SmPC)
Indication(s) in the EEA	Current: Nuvaxovid is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older.
	Proposed: Not applicable.
Dosage in the EEA	Current: Primary vaccination series: Individuals 12 years of age and older Nuvaxovid is administered intramuscularly (IM) 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.
	<u>Booster dose</u> <i>Booster dose in individuals 18 years of age and older</i> A booster dose of Nuvaxovid may be administered intramuscularly approximately 6 months after the second dose of the primary series in individuals 18 years of age and older (homologous booster dose). Nuvaxovid may be given as a booster dose in individuals 18 years of age and older following a primary series comprised of a mRNA vaccine or adenoviral vector vaccine (heterologous booster dose). The dosing interval for the heterologous booster dose is the same as that authorised for a booster dose of the vaccine used for primary vaccination.

Table Part I.1 Product(s) Overview

	<p>Proposed: <i>Booster Dose</i> <i>Booster dose in individuals 12 years of age and older</i> A booster dose of Nuvaxovid (0.5 ml) may be administered intramuscularly approximately 6 months after the primary series of Nuvaxovid in individuals 18 years of age and older and at least 5 months after the primary series in adolescents 12 through 17 years of age (homologous booster dose).</p>
<p>Pharmaceutical form(s) and strengths</p>	<p>Current: Dispersion for injection in multidose container of 10 doses of 0.5 mL. Each dose contains 5 µg SARS-CoV-2 spike protein and is adjuvanted with Matrix-M. The dispersion is colourless to slightly yellow, clear to mildly opalescent (pH 7.2).</p>
	<p>Proposed: Not applicable.</p>
<p>Is/will the product be subject to additional monitoring in the EU?</p>	<p>Yes</p>

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Indication:

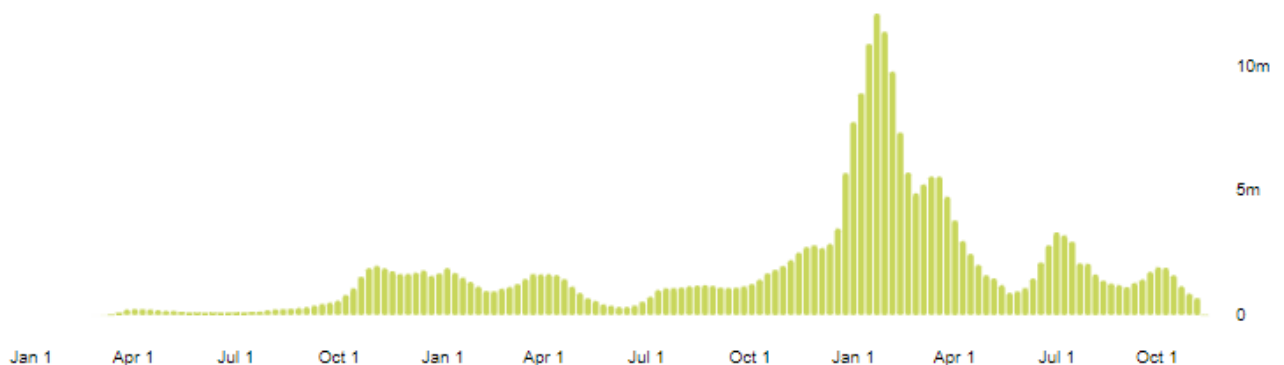
Active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older.

Incidence and prevalence:

At the end of 2019, a novel coronavirus was identified as the cause of a cluster of pneumonia cases in Wuhan, China. The virus rapidly spread, resulting in an epidemic throughout China, followed by a global pandemic. In February 2020, the World Health Organisation (WHO) designated the disease coronavirus disease 2019 or COVID-19. The virus that causes COVID-19 is designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

As of 14 November 2022, there were nearly 632 million confirmed cases of COVID-19 worldwide and over 6.5 million deaths (WHO 2022). In the WHO Region of Europe there were more than 262 million cases (Figure SI.1), and more than 2 million deaths.

Figure SI.1: COVID-19 Cases Reported Weekly in WHO Europe (1 January 2020 to 14 November 2022 (WHO 2022))



The reported case counts underestimate the overall burden of COVID-19, as only a fraction of acute infections which are diagnosed and reported. Seroprevalence surveys in the US and Europe have suggested that after accounting for potential false positives or negatives, the rate of prior exposure to SARS-CoV-2, as reflected by seropositivity, may exceed the incidence of reported cases by approximately 10-fold or more (Stringhini 2020; Havers 2020).

Demographics and Risk Factors

Individuals of both genders and all age groups can acquire SARS-CoV-2 infection. Men are more likely than women to suffer from severe COVID-19 that requires hospitalisation, intensive care, non-invasive and invasive mechanical ventilation, and death (Josa-Laorden 2021). The risk of hospitalization and death due to COVID-19 increases with age. Data from the United States demonstrated that the oldest adults (85+ years old) are up to 15 times as likely to be hospitalised and 340 times as likely to die compared to the 18 – 29 years old reference group (CDC 2022a). The risk of hospitalization in children under 5 years of age is similar to the 18 – 29-year-old reference group and

less for those aged 5 – 17 years. The risk for death is less than that of the reference group for the 0 – 4 and 5 – 17 year old age groups.

Adults of any age with certain underlying medical conditions are at increased risk for severe illness from the virus that causes COVID-19. Severe illness from COVID-19 is defined as hospitalisation, admission to the ICU, intubation, or mechanical ventilation. The most important underlying conditions that may increase the risk for COVID-19 severity include: cancer, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), heart conditions such as heart failure, coronary artery disease, or cardiomyopathies, immunocompromising conditions (e.g., Human Immunodeficiency Virus [HIV], tuberculosis, use of corticosteroids or other immunosuppressive medications, primary immunodeficiencies), sickle cell disease, smoking, and diabetes mellitus (CDC2022b; RIVM 2022; ECDC 2022a).

Impact on Socially Vulnerable Groups

In the EU/EEA prior to December 2019, there were an estimated 2.9 million residents in 43,000 long-term care facilities (LTCFs), representing approximately 0.7% of the total population. By May 2020, COVID-19-related deaths among LTCF residents accounted for 37 – 66% of all COVID-19-related deaths in EU/EEA countries (ECDC 2021).

A study conducted by the Dutch RIVM showed that access to regular health care had been limited, lifestyles had changed, and social life had been impoverished as a result of COVID-19 (RIVM 2020). The social effects of the COVID-19 crisis have a greater impact on vulnerable groups in society, such as lower-educated adults, young people, the elderly, and people with underlying health problems. Mental health was also under pressure due to the COVID-19 crisis. One-third of the population felt more despondent, and one-third felt more stressed and anxious during the crisis than before.

The Main Existing Treatment Options:

Management of Persons with COVID-19

Management of COVID-19 is based on best supportive care and emerging standard of care. Medications authorised for treatment of COVID-19 in the EU include antiviral medicines (i.e., Paxlovid and Veklury), monoclonal antibodies (i.e., Evusheld, Regkirona, RoActemra, Ronapreve, Xevudy), and an immunosuppressive medicine (i.e., Kineret) (EMA 2022a).

Prophylaxis

The following vaccines are authorized for use in the EU for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus: Comirnaty (BioNTech and Pfizer), Vaxzevria (AstraZeneca), Spikevax (Moderna), Nuvaxovid (Novavax), Jcovden (Janssen), COVID-19 vaccine (Valneva) and VidPrevtyn Beta (Sanofi Pasteur) (EMA 2022b).

In addition, two monoclonal antibodies (i.e., Evusheld and Ronapreve) are authorised for prevention of COVID-19 (EMA 2022a). General preventative measures include social distancing, face masks, and proper hygiene.

Primary Series

Everyone aged 5 years and over can get a 1st and 2nd dose of a COVID-19 vaccine. People aged 5 years and over who had a severely weakened immune system when they had their 1st or 2nd dose were offered an additional primary dose (NHS 2022).

As of 27 October 2022, 75.3% of the EU/EEA population had received at least one dose of a COVID-19 vaccine and 72.6% had completed the primary course (country range: 30.0 – 82.2%) (ECDC 2022a). Completion of the primary course was 83.3% among those 18 years and older (country range: 35.7 – 94.1%) and 90.9% among those 60 years and older (country range 38.4 – 100%).

Boosters

People aged 16 years and over, and some children aged 12 to 15 years, can also get a booster dose.

As of 27 October 2022, 53.9% of the EU/EEA population had received at least one booster dose and 7.7% had received a second booster dose (ECDC 2022a). Among those 18 years and older, 65.0% and 9.4% had received a first and second booster dose, respectively. Among those 60 years and older, 84.4% and 19.3% had received a first and second booster dose, respectively.

Clinical Manifestations and Natural History

Among persons who tested positive for COVID-19 but had no symptoms at the time of testing, the proportion who remained asymptomatic during follow-up ranged from 11.1% to 100%, with a median of 72.3% (Oran 2021).

Cough, myalgias, and headache are the most commonly reported symptoms of COVID-19 (Stokes 2020). Other symptoms include fever, dyspnea, sore throat, diarrhea, nausea/vomiting, loss of smell or taste, abdominal pain, and rhinorrhea. These symptoms may range from mild to critical.

Some patients with initially non-severe symptoms may progress over the course of about a week (Cohen 2020) with pneumonia, respiratory failure, cardiac and cardiovascular complications, thromboembolic complications, neurologic complications, inflammatory complications (including auto-antibody-mediated manifestations (Restivo 2020; Berzuini 2020), multiorgan failure (Mokthari 2020) and secondary infections. A fraction of patients who had COVID-19 who undergo a variable acute symptomatic phase of the disease continue with effects of the disease, including mental fog, delayed latent periods in recalling events of recent past, tachycardia, extreme fatigue, and inability to perform daily physical tasks (Baig 2021; Rubin 2020).

The clinical presentation in children is heterogeneous, including a wide spectrum of clinical features. Fever and cough are the most commonly reported presenting symptoms. Children predominantly contracted a mild form of infection but could be at risk of more severe outcomes. Among non-hospitalised children < 18 years of age, 89% experienced one or more typical symptoms of COVID-19, including fever, cough, shortness of breath, and 22% experienced all three (Burke 2020).

SARS-CoV-2 Variants

Viruses constantly change through mutation, and new variants of a virus are expected to occur. Sometimes new variants emerge and disappear. Other times, new variants persist. Numerous variants of the virus that causes COVID-19 are being tracked in the EU and globally during this pandemic.

Among the nine countries with an adequate volume of sequencing or genotyping (from 07 November to 20 November 2022), the estimated distribution of variants of concern or of interest, all of which are lineages of Omicron, was 52.7% (38.6 – 97.5% from nine countries) for BA.5, 37.0% (8.5 – 53.9% from seven countries) for BQ.1, 4.3% (0.7 – 25.9% from nine countries) for BA.2.75, 1.4% (0.3 – 3.7% from nine countries) for BA.4, and 1.3% (0.5 – 5.1% from nine countries) for BA.2 (ECDC 2022b).

Part II: Module SII - Non-clinical Part of the Safety Specification

No risks have been identified in the non-clinical testing programme, and the data support the proposed dose and regimen for human use (i.e., 5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant administered on Days 0 and 21 [+7 days]).

Studies across multiple species immunised with SARS-CoV-2 rS, including non-human primate models administered the intended human dose, have shown no evidence of vaccine-enhanced disease following challenge with live SARS-CoV-2 virus, even when administered at suboptimal vaccine doses (i.e., single doses and/or lower antigen/adjuvant doses). In a repeat-dose toxicity study in rabbits, 50 µg SARS-CoV-2 rS with or without 50 µg Matrix-M adjuvant was well tolerated with non-adverse findings limited to local injection site inflammation and serum chemical markers of inflammation, which were transient and considered consistent with immune system stimulation consequent to immunisation. Data from a developmental and reproductive toxicity study in rats indicate no adverse findings on fertility, pregnancy/lactation, or development of the embryo/foetus and offspring through post-natal Day 21. See [Table SII.1](#) for an overview of the non-clinical toxicology studies and the key findings.

Table SII.1: Non-Clinical Toxicology Studies

Study Number & Description (Status)	Animals (N)	Key Conclusions	Results Relevant to Human Use
Single-Dose Toxicity			
None performed	None performed	None performed	None performed
Repeat-Dose Toxicity			
<p>702-091 57-day repeat-dose Good laboratory practice (GLP) toxicity study of SARS-CoV-2 rS with Matrix-M Adjuvant (Complete)</p>	<p>NZW rabbits (n = 30/group)</p>	<p>SARS-CoV-2 rS with or without Matrix-M adjuvant was well tolerated with no effect on mortality, cage-side observations, physical examination findings, Draize scores of the injection sites, body weights, food consumption, body temperatures, ocular examination findings, absolute and relative organ weights, or macroscopic observations at necropsy.</p> <p>Effects on clinical pathology parameters (fibrinogen, CRP, and/or globulin), which resolved during the recovery interval, and histopathology (subacute inflammation at injection sites and adjacent tissue), which were decreased at the recovery interval, were consistent with immune stimulation following administration of a vaccine.</p> <p>Anti-S IgG results confirmed vaccine delivery and demonstrated 100% seroconversion.</p>	<p>This non-clinical repeat-dose toxicity study with SARS-CoV-2 rS did not indicate any adverse vaccine-related effects. All vaccine-related effects noted were considered to reflect a normal, immunologic response to the vaccine. There were no findings observed that would raise a specific safety concern for the use of SARS-CoV-2 rS with Matrix-M adjuvant in humans.</p>
Genotoxicity			
<p>20#312 Non-GLP bacterial reverse mutation assay (Complete)</p>	<p>Not applicable</p>	<p>Matrix-M adjuvant at concentrations up to 1000 µg per plate was negative (non-mutagenic).</p>	<p>This non-clinical toxicity study with Matrix-M adjuvant did not indicate any mutagenicity in vitro. There were no findings observed that would raise a specific safety concern for the use of Matrix-M adjuvant in humans.</p>
<p>20#313 Non-GLP mammalian chromosome aberration assay (Complete)</p>	<p>Not applicable</p>	<p>Matrix-M adjuvant at concentrations up to 100 µg/mL was negative with no significant increases observed for the induction of micronuclei.</p>	<p>This non-clinical toxicity study with Matrix-M adjuvant did not indicate any genotoxicity in vitro. There were no findings observed that would raise a specific safety concern for the use of Matrix-M adjuvant in humans.</p>
<p>20#316 GLP bacterial reverse mutation assay (Complete)</p>	<p>Not applicable</p>	<p>Matrix-M adjuvant at concentrations up to 4.4 mg/mL was non-mutagenic for all tester strains in the presence or absence of S9 rat liver.</p>	<p>This non-clinical toxicity study with Matrix-M adjuvant did not indicate any mutagenicity in vitro. There were no findings observed that would raise a specific safety concern for the use of Matrix-M adjuvant in humans.</p>

Table SII.1: Non-Clinical Toxicology Studies

Study Number & Description (Status)	Animals (N)	Key Conclusions	Results Relevant to Human Use
<p>20#317 GLP mammalian cell micronucleus assay (Complete)</p>	<p>Not applicable</p>	<p>Matrix-M adjuvant at concentrations up to 4.4 mg/mL was negative for the induction of micronuclei in the presence and absence of the exogenous metabolic activation system.</p>	<p>This non-clinical toxicity study with Matrix-M adjuvant did not indicate any genotoxicity in vitro. There were no findings observed that would raise a specific safety concern for the use of Matrix-M adjuvant in humans.</p>
<p>Reproductive toxicity</p>			
<p>702-096-PILOT Immune response (Complete)</p>	<p>Sprague Dawley rat (n= 4/sex/group)</p>	<p>Both female and male rats generated strong anti-S IgG titers supporting the initiation of the GLP developmental and reproductive toxicology study in this animal model.</p>	<p>This pilot non-clinical toxicity study of SARS-CoV-2 rS with Matrix-M adjuvant did not indicate any adverse vaccine related effects. All vaccine-related effects noted were considered to reflect a normal, immunologic response to the vaccine. There were no findings observed that would raise a specific safety concern for the use of SARS-CoV-2 rS with Matrix-M adjuvant in humans.</p>
<p>702-096 GLP developmental and reproductive toxicity study of SARS-CoV-2 rS (Complete)</p>	<p>Sprague Dawley rat (n = 50/sex/group)</p>	<p>Administration of SARS-CoV-2 rS with Matrix-M adjuvant or Matrix-M adjuvant alone had no effect on mortality, physical examinations, cage-side observations, body weights, body weight changes, estrus cyclicity, or food consumption during the pre-cohabitation, gestation, or developmental periods in dams.</p> <p>In the uterine cohort, there was no difference between foetal body weights, survival, or foetal external, visceral, or skeletal exams.</p> <p>In the developmental cohort, there were no differences in number of male and female pups, pup body weights, survival, litter size and sex, developmental markers, or gross pathology findings.</p> <p>SARS-CoV-2 rS with Matrix-M adjuvant elicited robust anti-S IgG titers with a 100% seroconversion rate. Maternal anti-S IgG antibodies were detected in both foetal and pup samples confirming transfer of antibodies during gestational and postnatal stages of development; albeit pups exhibited significantly higher levels of maternal antibodies than foetuses.</p>	<p>This non-clinical developmental and reproductive toxicity study of SARS-CoV-2 rS with Matrix-M adjuvant did not indicate any adverse vaccine related effects. All vaccine-related effects noted were considered to reflect a normal, immunologic response to the vaccine. There were no findings observed that would raise a specific safety concern for the use of SARS-CoV-2 rS with Matrix-M adjuvant in humans.</p>

The Adjuvant

Matrix-M is a saponin-based adjuvant manufactured by mixing defined, partially purified extracts of the bark of the *Quillaja saponaria* Molina tree, termed Fraction-A and Fraction-C.

Saponins are a class of chemical compounds found naturally in various plant species, with uses in a variety of applications including agriculture, animal feeds, human foods and beverages, mining, and commercial veterinary vaccines (e.g., vaccines against foot-and-mouth disease, bovine mastitis, feline leukemia, and equine influenza). The adjuvanting property of saponins to boost both humoral and cellular immune responses to antigens that are generally poor immunogens in veterinary vaccines has precipitated the exploration of saponin-based adjuvants in human vaccines as well. The proposed mode of action for saponin-based adjuvants is through a combination of activities including recruitment and activation of innate immune cells, rapid antigen delivery to antigen-presenting cells, and enhanced antigen presentation via both major histocompatibility complex (MHC) I and MHC II molecules in the draining lymph nodes.

The toxicology data obtained in animal studies to evaluate Matrix-M adjuvant, alone or co-administered with different vaccine antigens, does not demonstrate relevant systemic or organ-specific toxicities and Matrix-M adjuvant administration was generally well tolerated. There were transient and inconsistent reductions in body weight and red cell mass parameters, as well as temperature elevations in some studies but these findings tended to resolution following the recovery period. Local injection site inflammation and regional lymph node hyperplasia consistent with active immunisation were present in acute necropsies but showed resolution at recovery time points.

Part II: Module SIII - Clinical Trial Exposure

The following studies are planned or ongoing at the DLP of this RMP:

- 2019nCoV-101 Part 2 (Australia and United States): A 2-Part, Phase 1/2, Randomized, Observer-Blinded Study to Evaluate the Safety and Immunogenicity of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine (SARS-CoV-2 rS) With or Without Matrix-M Adjuvant in Healthy Subjects. *Note: This is Part 2 (Phase 2) of 2019nCoV-101 evaluating participants 18 to 84 years of age. The vaccine was administered with adjuvant and evaluated as a co-formulated drug product (DP) (as in the remaining Phase 2 and Phase 3 studies). This study is also evaluating the safety and immunogenicity of a single booster dose of NVX-CoV2373 administered approximately 6 months after the primary vaccination series.*
- 2019nCoV-501 (South Africa): A Phase 2a/b, Randomized, Observer-Blinded, Placebo-Controlled Study to Evaluate the Efficacy, Immunogenicity, and Safety of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine with Matrix-M Adjuvant in South African Adult Subjects Living without Human Immunodeficiency Virus (HIV); and Safety and Immunogenicity in Adults Living with HIV. *Note: This study is also evaluating the safety and immunogenicity of a single booster dose of NVX-CoV2373 administered approximately 6 months after the primary vaccination series, as well as crossover dosing of active vaccine for participants who received placebo in the initial set of vaccinations.*
- 2019nCoV-302 (UK): Phase 3, Randomised, Observer-Blinded, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine with Matrix-M Adjuvant in Adult Participants 18-84 Years of Age in the United Kingdom.

- 2019nCoV-505 (South Africa): A Phase 2, Randomized, Observer-Blinded Study to Evaluate the Safety and Immunogenicity of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine (SARS-CoV-2 rS) With Matrix-M™ Adjuvant in People Living With HIV.
- 2019nCoV-311(Australia): A Phase 3, Randomized, Observer Blinded Study to Evaluate the Safety and Immunogenicity of Two Booster Doses of the NVX-CoV2515 Vaccine in Adults Previously Vaccinated with Other COVID-19 Vaccines.
- 2019nCoV-301 (North America): 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 with Matrix-M Adjuvant in Adult Participants ≥ 18 years with a Pediatric Expansion in Adolescents (12 to < 18 Years).

The following study was completed:

- 2019nCoV-101 Part 1 (Australia): A 2-Part, Phase 1/2, Randomized, Observer-Blinded Study to Evaluate the Safety and Immunogenicity of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine (SARS-CoV-2 rS) With or Without Matrix-M Adjuvant in Healthy Subjects. *Note: This is Part 1 (Phase 1 first-in-human) of 2019nCoV-101 evaluating participants 18 to 59 years of age. The vaccine was administered with and without adjuvant and evaluated as a bedside-mixed antigen and adjuvant.*

[Table SIII.1](#) presents the number of adult participants (≥ 18 years of age) receiving the primary vaccination series with the SARS-CoV-2 rS vaccine at any dose level. The pooled safety analysis comprises 30,058 participants who have received the 5 μg SARS-CoV-2 rS + 50 μg Matrix-M adjuvant dose (dose level intended for licensure) across the SARS-CoV-2 rS clinical development programme, with over 96% of the participants (28,963) receiving both doses of trial vaccine.

[Table SIII.2](#) presents exposure by age group and gender and [Table SIII.3](#) presents exposure by the ethnic origin and race in adult participants (≥ 18 years of age) receiving the primary vaccination series.

[Table SIII.4](#), [Table SIII. 5](#), [Table SIII.6](#), and [Table SIII.7](#) present the exposure of adolescent participants 12 through 17 years of age following primary vaccination in the Paediatric Expansion of Study 2019nCoV-301.

[Table SIII. 8](#), [Table SIII. 9](#), [Table SIII. 10](#), and [Table SIII.11](#) present exposure in adult participants (≥ 18 years of age) administered a homologous booster dose in clinical studies 2019nCoV-101 (Part 2), 2019nCoV-501, and 2019nCoV-301.

[Table SIII.12](#), [Table SIII.13](#), [Table SIII.14](#), and [Table SIII.15](#) present exposure of adolescent participants 12 through 17 years of age who were administered a homologous booster dose in the Paediatric Expansion of Study 2019nCoV-301.

Table SIII.1: Exposure in Adult Participants (≥ 18 Years of Age) - Primary Vaccination Series

Dose Antigen/Dose Adjuvant	Participants Receiving 1 Dose	Participants Receiving 2 Doses	Total Number of Participants	Total Number of Doses
5 µg/50 µg	1,095	28,963	30,058	59,021
25 µg/0 µg	0	25	25	50
25 µg/50 µg	290	278	568	846
Total	1,385	29,266	30,651	59,917

Table SIII.2: Age Group and Gender in Adult Participants (≥ 18 Years of Age) - Primary Vaccination Series*

Age Group	Total Subjects	Participants		Total Doses	Number of Doses	
		Male	Female		Male	Female
≥ 18 - < 65	25,282	13,225	12,057	49,737	26,000	23,737
≥ 65 - < 74	3,833	2,069	1,764	7,474	4,036	3,438
≥ 74 - < 85	922	520	402	1,771	995	776
≥ 85	21	12	9	39	21	18
Total	30,058	15,826	14,232	59,021	31,052	27,969

*At least one dose 5 µg/50 µg

Table SIII.3: Ethnic Origin and Race in Adult Participants (≥ 18 Years of Age) - Primary Vaccination Series

Ethnic Origin	Participants	Number of Doses
Hispanic/Latino	4,463	8,765
Not Hispanic/Latino	24,647	48,382
Not Reported	780	1,540
Unknown	161	320
Missing	7	14
Total	30,058	59,021
Race	Participants	Number of Doses
White	22,415	44,038
Black or African American	4,417	8,653
Asian	1,119	2,189
American Indian or Alaska Native	1,322	2,602
Native Hawaiian or Other Pacific Islander	58	113
Multiple	463	910
Not Reported	209	408
Other	43	84
Missing	12	24
Total	30,058	59,021

*At least one dose 5 µg/50 µg

Table SIII.4: Exposure by Age Group in Participants 12-17 Years of Age in 2019nCoV-301 Paediatric Expansion Study – Primary Vaccination Series

Age	Participants Receiving 1 Dose	Participants Receiving 2 Doses	Total Participants
12 to < 15 years of age	14	984	998
15 to < 18 years of age	8	481	489
Total	22	1,465	1,487

Table SIII.5: Age Group and Gender in Participants 12-17 Years of Age in 2019nCoV-301 Paediatric Expansion Study – Primary Vaccination Series

Age group (years)	Total Participants	Participants		Total Doses	Number of Doses	
		M	F		M	F
12 to < 15	998	508	490	1,982	1,008	974
15 to < 18 years of age	489	248	241	970	492	478
Total	1,487	756	731	2,952	1,500	1,452

Table SIII.6: Exposure by Gender in Participants 12-17 Years of Age in 2019nCoV-301 Paediatric Expansion Study – Primary Vaccination Series

Gender	Participants Receiving 1 Dose	Participants Receiving 2 Doses	Total Number of Participants
Male	12	744	756
Female	10	721	731
Total	22	1,465	1,487

Table SIII.7: Ethnic Origin and Race in Participants 12-17 Years of Age in 2019nCoV-301 Paediatric Expansion Study – Primary Vaccination Series

Race	Subjects	Number of Doses
White	1,115	2,216
Black or African American	202	401
American Indian or Alaska Native	32	60
Asian	43	86
Mixed origin	82	164
Native Hawaiian or Other Pacific Islander	3	6
Not reported	10	19
Total	1,487	2,952
Ethnicity	Subjects	Number of doses
Not Hispanic or Latino	1,208	2,404
Hispanic or Latino	274	538
Not reported	2	4
Unknown	3	6
Total	1,487	2,952

Table SIII.8: Exposure in Adult Participants (≥ 18 Years of Age) in Clinical Studies 2019nCoV-101 (Part 2), 2019nCoV-301, and 2019nCoV-501 - Homologous Booster Vaccination

Participants Receiving a Booster Dose	Total Number of Doses
14,780	44,298

Table SIII.9: Age Group and Gender in Adult Participants (≥ 18 Years of Age) in Clinical Studies 2019nCoV-101 (Part 2), 2019nCoV-301, and 2019nCoV-501 - Homologous Booster Vaccination

Age Group	Total Participants	Participants		Total Doses	Number of Doses	
		M	F		M	F
≥ 18 - < 65	12,930	6,665	6,265	38,750	19,974	18,776
≥ 65 - < 74	1,490	759	731	4,467	2,274	2,193
≥ 74 - < 85	347	190	157	1,041	570	471
≥ 85	13	6	7	40	19	21
Total	14,780	7,620	7,160	44,298	22,837	21,461

Table SIII.10: Exposure by Study in Adult Participants (≥ 18 Years of Age) in Clinical Studies 2019nCoV-101 (Part 2), 2019nCoV-301, and 2019nCoV-501 - Homologous Booster Vaccination*

Study	Participants Receiving 1 Dose	Participants Receiving 2 Doses	Participants Receiving 3 Doses	Participants Receiving 4 Doses	Participants Receiving 5 Doses	Total Number of Participants
101 part 2	0	0	105	0	0	105
501	0	20	1878	0	0	1898
301	16	9	12734	17	1	12777
Total	16	29	14717	17	1	14780

*Participants received 1 dose of NVX-CoV2373 during the booster period.

Table SIII.11: Ethnic Origin and Race in Adult Participants (≥ 18 Years of Age) in Clinical Studies 2019nCoV-101 (Part 2), 2019nCoV-301 and 2019nCoV-501 - Homologous Booster Vaccination

Ethnic Origin	Participants	Number of Doses
Hispanic/Latino	2,766	8,296
Not Hispanic/Latino	11,976	35,888
Not Reported	23	69
Unknown	14	42
Missing	1	3
Total	14,780	44,298
Race	Participants	Number of doses
White	9,390	28,154
Black or African American	3,612	10,811
Asian	526	1,576
American Indian or Alaska Native	834	2,503
Native Hawaiian or Other Pacific Islander	28	84
Multiple	275	825
Not Reported	82	247
Other	29	86
Missing	4	12
Total	14,780	44,298

Table SIII.12: Exposure in Participants 12 -17 Years of Age in 2019nCoV-301 Paediatric Expansion Study - Homologous Booster Vaccination*

Participants Receiving a Booster Dose	Total Number of Doses
1499	4489

*Participants who received a booster vaccination

Table SIII.13: Age Group and Gender in Participants 12-17 Years of Age in 2019nCoV-301 Paediatric Expansion Study - Homologous Booster Vaccination*

Age group (years)	Total Participants	Participants		Total Doses	Number of Doses	
		M	F		M	F
12 - < 15	1020	559	461	3054	1673	1381
15 - < 18	479	247	232	1435	741	694
Total	1499	806	693	4489	2414	2075

*Participants who received a booster vaccination

Table SIII.14: Exposure by Gender in Participants 12 -17 Years of Age in 2019nCoV-301 Paediatric Expansion Study – Homologous Booster Vaccination*

Gender	Participants Receiving 1 Dose	Participants Receiving 3 Doses	Total Number of Participants
Male	2	804	806
Female	2	691	693
Total	4	1495	1499

*Participants who received a booster vaccination

Table SIII.15: Ethnic Origin and Race in Participants 12-17 Years of Age in 2019nCoV-301 Paediatric Expansion Study - Homologous Booster Vaccination*

Ethnic Origin	Participants	Number of Doses
Hispanic/Latino	276	828
Not Hispanic/Latino	1220	3652
Not Reported	1	3
Unknown	2	6
Total	1499	4489
Race	Participants	Number of doses
White	1096	3282
Black or African American	219	655
Asian	53	159
American Indian or Alaska Native	40	120
Native Hawaiian or Other Pacific Islander	5	15
Multiple	77	231
Not Reported	9	27
Other	0	0
Total	1499	4489

* Participants who received a booster vaccination

Additional Exposure to the Adjuvant (Matrix-M)

Matrix-M adjuvant (M1 or M2 formulations, which differ in the ratio of Fractions-A and -C) has also been administered to over 4,000 human subjects in other clinical trials (not including the above COVID-19 studies), sponsored by Novavax or other collaborating entities. Over 3,500 of these subjects have received vaccines containing the Matrix-M adjuvant. Notably, 2,574 adult subjects have

been exposed to 50 or 75 µg Matrix-M adjuvant in clinical trials with other nanoparticle vaccine antigens produced using the same manufacturing platform technology as the SARS-CoV-2 rS antigen (respiratory syncytial virus [RSV]) F, Ebola, and Influenza Hemagglutinin) with longer-term safety data available through 6 months or 1 year.

In the current product, the Matrix-M formulation in the 50 µg dose is included, and throughout this document Matrix-M adjuvant will be used as the name for the adjuvant.

Part II: Module SIV – Populations not Studied in Clinical Trials

Detailed descriptions of all inclusion and exclusion criteria for clinical studies are provided in the individual study protocols.

SIV.1 Exclusion Criteria in Clinical Studies within the Development Programme

Table SIV.1: Exclusion Criteria in Clinical Studies within the Development Programme

Criterion	Reason for Exclusion	Included as Missing Information	Rationale (if not included as missing information)
Any acute (within 14 days prior to the study vaccination) or chronic clinically significant illness and/or fever	Allowance of these conditions would confound assessment of safety, and these febrile participants might already be infected with SARS-CoV-2. It is common medical practice to not administer vaccines in febrile participants. Febrile participants with minor illnesses could be enrolled at the discretion of the investigator. This is managed with the product prescribing information.	No	It is common medical practice to not administer vaccines in febrile participants as this would not allow accurate assessment of whether the vaccine induces fever.
Previous clinical or laboratory-confirmed diagnosis of COVID-19	Studies 501, 301, and 302 excluded participants with laboratory-confirmed COVID-19 because these participants would confound assessment of efficacy, immunogenicity, and safety.	No	Safety in study participants with prior infection will be assessed in the pivotal studies.
Any autoimmune or immunodeficiency disease/condition or being treated with a biologic therapy	Immunocompromised participants may have impaired immune responses to vaccines and would therefore limit the ability to demonstrate efficacy, which is the primary pivotal endpoint.	Yes	Not applicable; use in individuals with autoimmune or inflammatory disorders is included as missing information.

Table SIV.1: Exclusion Criteria in Clinical Studies within the Development Programme

Criterion	Reason for Exclusion	Included as Missing Information	Rationale (if not included as missing information)
Known disturbance of coagulation; Bleeding disorder (e.g., factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following intramuscular (IM) injections or venipuncture (Study 302)	Participants have a potential risk of hematoma due to the puncture of the deep tissues. Allowance of these conditions would confound assessment of safety.	No	It is common medical practice not to administer a product by the IM route in participants with coagulopathy or bleeding disorders although the use of a needle with proper gauge can decrease the risk.
Drugs or alcohol abuse or drug addiction within one year prior to the first study vaccination.	Participants with drug or alcohol abuse or drug addiction within 1 year prior to the first study vaccination are considered less likely to comply with study procedures and complete the long-term safety follow-up required by the study protocols.	No	Study 302: Suspected or known current alcohol or drug dependence. While these participants were to be excluded per the protocol, participants are not always forthcoming regarding this aspect of their medical history and it is assumed that a not inconsequential number were actually enrolled.
Allergies to products contained in the investigational product. Any history of anaphylaxis to any prior vaccine (Study 302)	Participants with medical history significant for allergic reactions following vaccines are at increased risk for hypersensitivity reactions when receiving another vaccine.	No	It is common medical practice to not administer a new vaccine in participants who have a history of significant allergic reactions to other vaccines.
Pregnant, breastfeeding, or planning to become pregnant during the study	To avoid use in a vulnerable population. Clinical development generally does not initially investigate benefit/risk in pregnant women.	Yes	Not applicable; use in pregnancy and while breastfeeding is included as missing information.

Table SIV.1: Exclusion Criteria in Clinical Studies within the Development Programme

Criterion	Reason for Exclusion	Included as Missing Information	Rationale (if not included as missing information)
<p>Received any live vaccine within 4 weeks or any vaccine (excluding influenza) within 2 weeks prior to first study vaccination or any licensed influenza vaccine within 1 week prior to first study vaccination or plans to receive any vaccine from these time periods until 28 days after second study vaccination.</p> <p>NOTE: An influenza co-administration sub-study of Study 302 was conducted in which approximately 400 participants received a single dose of seasonal influenza vaccine at the same time as first study vaccination. In addition, a licensed seasonal influenza vaccine may be given 7 days after each vaccination but should not be given within 7 days prior to second vaccination (Study 302)</p> <p>Received influenza vaccination or any other adult vaccine within 4 days prior to or within 7 days after either study vaccination (Study 301)</p>	<p>Allowance of this condition would confound assessment of safety and efficacy.</p>	<p>Yes</p>	<p>Not applicable; interaction with other vaccines is included as missing information.</p>
<p>Participant requires the use of continuous oxygen therapy or any oxygen therapy while awake or is anticipated to require daytime oxygen therapy during the course of the study. (Study 302)</p>	<p>Participants requiring the use of continuous oxygen therapy or any oxygen therapy while awake and with a baseline oxygen saturation less than 95% were excluded due to feasibility issues regarding the ability to characterize their disease severity while on oxygen.</p>	<p>No</p>	<p>While participants requiring oxygen therapy were excluded, participants with stable COPD and other pulmonary diseases were included.</p>
<p>Paediatric participants < 12 years of age</p>	<p>Clinical development programmes generally investigate first the benefit-risk in adults.</p> <p>In adults, the risk of symptomatic and severe COVID-19 usually seems higher.</p>	<p>No</p>	<p>A paediatric investigation plan has been agreed with the Agency on 15 October 2021.</p>

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

Rare Adverse Drug Reactions

With the vaccine-exposed study population (over 30,000 participants), events with a frequency of 1/10,000 persons or 0.01% can be detected. Most rare AEs of special interest (AESIs) for post-marketing safety surveillance have incidence rates lower than 2/10,000 persons or 0.02%.

Adverse Drug Reactions of Long Latency

The primary series vaccination regimen is two doses administered 21 days apart (+ 7 days), so there is no prolonged nor cumulative exposure to the vaccine. The pooled safety analysis was performed once the median follow-up duration of at least 2 months after vaccination was completed. The median duration of follow-up for the adult participants was 78 days post-dose 2, with 32,993 (66%) participants of all the total number of participants (active and placebo) completing more than 2 months follow-up post-dose 2. However, the planned duration of follow-up in all clinical trials except Study 301 is up to 1 year; Study 301 will follow participants up to 2 years. In the paediatric expansion study 2019nCoV-301, the duration of follow-up for paediatric participants 12 to < 18 years of age was at least 60 days and may continue until 2 years. Therefore, there has been limited opportunity to observe potential adverse drug reactions (ADRs) that might occur with more prolonged latency beyond the 2-year follow-up period.

Studies 2019nCoV-101 (Part 2) and 2019nCoV-501 evaluated the safety and immunogenicity of a single booster dose of NVX-CoV2373 administered to adults approximately 6 months after the primary vaccination series. Safety and immunogenicity data are available for both studies with follow-up ongoing for 6 months. The paediatric expansion of Study 2019nCoV-301 evaluated the safety and immunogenicity of a single booster dose of NVX-CoV2373 administered to participants 12 to < 18 years of age no less than 5 months after the primary vaccination series. Safety and immunogenicity data are available for this study with follow-up ongoing through 2 years post immunization.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.2: Exposure of Special Populations included or Not in Clinical Trial Development Programme

Type of Special Population	Exposure
Pregnant women	Pregnant women were excluded from the clinical development programme.
Breastfeeding women	Breastfeeding women were not included in clinical development programme. It is unknown whether NVX-CoV2373 is excreted in human milk.
Elderly population	Clinical studies of the vaccine included 4,776 participants 65 years of age and over.
Paediatric population < 12 years of age	The safety and efficacy of Nuvaxovid in children aged less than 12 years have not yet been established.
Patients with relevant comorbidities: Patients with hepatic impairment Patients with renal impairment Patients with cardiovascular impairment Immunocompromised patients Patients with a disease severity different from inclusion criteria in clinical trials	Healthy participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalisation for worsening disease during the 6 weeks before enrolment, were included. This allowed enrolment of a proportion of participants with common comorbidities such as cardiovascular diseases including hypertension, chronic pulmonary diseases, asthma, chronic liver disease, body mass index (BMI) > 30 kg/m ² , participants with CKD, and participants with varying disease severity. Participants with potential immunodeficient status were not specifically included in the study population.
Population with relevant different ethnic origin	Refer to Table SIII.3 , Table SIII.7 , Table SIII.11 , and Table SIII.15 for exposure information by ethnic origin from the studies.
Subpopulations carrying relevant genetic polymorphisms	Not applicable

Part II: Module SV – Post-authorisation experience

SV.1 Post-authorisation exposure

Nuvaxovid was first authorised for emergency use in the EU on 20 December 2021. Since that time, Nuvaxovid has received conditional/emergency use authorisation in multiple countries and regions in collaboration with partners. Please refer to Summary Safety Report (SSR) #10 (DLP – 15 November 2022) for details of the Nuvaxovid post-authorisation experience globally.

SV.1.1 Method used to calculate exposure

Not applicable.

SV.1.2 Exposure

Distribution and vaccine administration data (where available) were used to approximate cumulative post-authorisation exposure. To comprehensively represent exposure, [Table SV.1.2](#) includes distribution of COVOVAX, a vaccine with the same active ingredients as Nuvaxovid that is developed and marketed in partnership with Serum Institute of India PVT. LTD (SIPL).

Cumulatively, 103,214,420 NVX-CoV2373 doses (93,890,270 Nuvaxovid and 9,324,150 COVOVAX doses) were distributed globally. A total of 2,266,287 Nuvaxovid doses were administered in Australia, Canada, EU, Israel, Japan, New Zealand, Singapore, South Korea, Switzerland, Taiwan and the USA and 26,181 COVOVAX doses were administered in India (as of 17-Nov-2022).

Table SV.1.2 Cumulative Exposure Data (Distributed and Administered) from Post-Authorisation Experience Presented by Region

Region/License Partner (LP)	Total Doses Administered	Total Doses Distributed
Australia (Bioelect Pty Ltd.) ^a	228,515	15,776,600
Canada (NVX) ^a	10,930	9,724,000
EU (NVX) ^a	354,959	49,572,190
India (SIPL) ^b	26,181	116,150
Indonesia (SIPL) ^b	Not applicable	9,008,000
Israel (Medicalix/Freyr) ^a	5	1,000,000
Japan (Takeda) ^a	242,844	6,997,110
New Zealand (Bioelect New Zealand Ltd.) ^a	6,659	2,007,600
Singapore (PharmaEng Technology Pte Ltd) ^a	18,073	534,000
South Korea (SK Bioscience) ^a	878,983	2,932,470
Switzerland (NVX) ^a	1,639	102,000
Taiwan (NVX) ^a	473,106	1,008,000
Thailand (SIPL) ^b	Not applicable	200,000
UK (NVX) ^a	Not applicable	1,000,000
USA (NVX) ^a	50,574	3,236,300
Nuvaxovid total	2,266,287	93,890,270
COVOVAX total	26,181	9,324,150

^a Distributed as Nuvaxovid

^b Distributed as COVOVAX

Part II: Module SVI – Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

The potential for misuse and/or counterfeit of COVID-19 vaccines is considered unlikely but cannot be excluded.

Part II: Module SVII – Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

All safety data available from the NVX-CoV2373 clinical development programme have been evaluated in order to formulate the important safety concerns described within this RMP.

The safety concerns presented in the initial EU RMP v1.0 are listed in [Table SVII.1](#).

Table SVII.1: Summary of Safety Concerns in the Initial RMP Submission

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

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Not all adverse reactions for the vaccine are considered to meet the level of importance/severity compared to the condition to be prevented necessitating inclusion in the list of safety concerns in the RMP.

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal and temporary clinical impact on patients (in relation to the severity of the disease prevented):

- Injection site tenderness, injection site pain, injection site redness, injection site swelling, injection site pruritus
- Fatigue
- Malaise
- Headache
- Myalgia
- Arthralgia
- Nausea
- Vomiting
- Pyrexia
- Chills
- Pain in extremity
- Pruritus
- Rash
- Lymphadenopathy
- Erythema

- Urticaria
- Hypertension

Known risks that do not impact the risk-benefit profile:

- Anaphylaxis

Further considerations for COVID-19 vaccines

Reactogenicity (local and systemic)

In accordance with the European Medicines Agency (EMA) requirements (Consideration on core RMP requirements for COVID-19 vaccines guidance), the reactogenicity profile of NVX-CoV2373 is described below for local and systemic reactions, including observed differences between ages (younger and older groups) and after any dose of NVX-CoV2373. The observed differences do not impact the safety profile of the NVX-CoV2373.

Primary series

Participants 18 years of age and older

Local injection site reactions: Injection site tenderness and injection site pain were reported in clinical studies as very commonly ($\geq 1/10$) occurring ADRs following IM injection of NVX-CoV2373. Injection site redness/injection site erythema and injection site swelling were commonly reported ($\geq 1/100$ to $< 1/10$) following IM injection. Injection site pruritus was uncommonly reported ($\geq 1/1,000$ to $< 1/100$). Local adverse reactions were generally mild or moderate in severity with a median duration of less than or equal to 2 days following vaccination. Specific guidance on the administration of Nuvaxovid for healthcare professionals (HCPs) is provided in the Summary of Product Characteristics (SmPC), and this is fully aligned with standard clinical practice for the management of local injection site reactions following immunisation.

Systemic reactions: Systemic reactions including fatigue, malaise/influenza-like illness, headache, myalgia, arthralgia, nausea, and vomiting were reported in clinical studies as very commonly occurring ADRs ($\geq 1/10$). Pyrexia, chills, and pain in extremity were observed as commonly reported ($\geq 1/100$ to $< 1/10$) ADRs in clinical studies. Pruritus, rash, lymphadenopathy, erythema, urticaria, and hypertension were uncommonly reported ($\geq 1/1,000$ to $< 1/100$). These systemic ADRs were usually mild to moderate in severity with a median duration of less than or equal to 1 day following vaccination. These ADRs are listed in the Nuvaxovid SmPC. These risks are considered non-serious and have minimal clinical impact.

Overall, there was a higher incidence of adverse reactions in younger age groups: the incidence of injection site tenderness, injection site pain, fatigue, myalgia, headache, malaise, arthralgia, and nausea or vomiting was higher in adults aged 18 to < 65 years than in those aged 65 years and above 65. Local and systemic adverse reactions were more frequently reported after Dose 2 than after Dose 1.

Participants 12 through 17 years of age

The safety of NVX-CoV2373 in participants 12 through 17 years of age was evaluated in an interim analysis of the paediatric expansion portion of an ongoing Phase 3 multicentre, randomised, observer-

blinded, placebo-controlled study. Safety data was collected in 2,232 participants 12 through 17 years of age, with and without evidence of prior infection, in the US who received at least one dose of NVX-CoV2373 (n = 1,487) and placebo (n = 745). Demographic characteristics were similar among participants who received NVX-CoV2373 and those who received placebo.

Local injection site reactions: The most frequent local adverse reactions occurring after any dose of IM injection of NVX-CoV2373 were injection site tenderness, injection site pain, injection site swelling, and injection site redness. Local adverse reactions were usually mild to moderate in severity with a median duration of less than or equal to 2 days.

Systemic reactions: The most frequent systemic adverse reactions occurring after any dose of NVX-CoV2373 were headache, myalgia, fatigue, malaise, nausea or vomiting, arthralgia, and pyrexia. Adverse reactions were usually mild to moderate in severity with a median duration of less than or equal to 1 day for systemic events following vaccination.

Booster dose

Participants 18 years of age and older

Following homologous boosting vaccination in study 2019nCoV-101 (Part 2), the most frequent solicited adverse reactions were injection site tenderness, fatigue, injection site pain, muscle pain, malaise, headache, joint pain, and fever with a median duration of 1 to 3 days following vaccination.

Solicited adverse reactions were not assessed after homologous boosting vaccination in study 2019nCoV-501.

The safety of a booster dose of Novavax COVID-19 Vaccine (recombinant, adjuvanted) was evaluated in the ongoing study 2019nCoV-301. Overall, 12,777 participants received a booster dose of Novavax COVID-19 Vaccine (recombinant, adjuvanted) at least 6 months after the two-dose primary series. The safety analyses included evaluation of solicited local and systemic adverse reactions within 7 days after a booster dose for participants who completed the electronic diary (n = 10,137). The most frequent solicited adverse reactions were injection site pain/tenderness, fatigue/malaise, muscle pain, headache, and joint pain.

Participants 12 through 17 years of age

The safety of a booster dose of Novavax COVID-19 Vaccine (recombinant, adjuvanted) was evaluated in the pediatric expansion portion of the ongoing study 2019nCoV-301. A total of 1,499 participants received a booster dose of Novavax COVID-19 Vaccine (recombinant, adjuvanted) approximately 9 months after receiving Dose 2 of the primary series. A subset of 220 participants who received the booster dose of Novavax COVID-19 Vaccine (recombinant, adjuvanted) were evaluated for solicited adverse reactions within 7 days after the booster dose (Ad Hoc Booster Safety Analysis Set). The most frequent solicited adverse reactions were tenderness, pain, headache, fatigue, muscle pain, malaise, and nausea/vomiting with a median duration of 1 to 2 days following vaccination.

Aspects of the formulation

Adjuvant:

NVX-CoV2373 with Matrix-M adjuvant is currently being evaluated in 5 ongoing clinical trials. To supplement the lack of available long-term safety data (≥ 6 months) in the ongoing clinical trials of NVX-CoV2373 with Matrix-M adjuvant, an integrated analysis of safety was performed in 2,574 adult participants 18 years of age and older across 5 Novavax-sponsored clinical trials (EBOV-H-101, tNIV-E-101, qNIV-E-201, qNIV-E-301 and RSV-E-205) of other recombinant nanoparticle vaccine antigens using the same manufacturing platform technology as NVX-CoV2373 administered with the same Matrix-M adjuvant with safety follow-up ranging from 6 months to 1 year. For this integrated analysis, short-term safety data (solicited local and systemic treatment emergent adverse events [TEAEs] and unsolicited TEAEs) were summarised for each individual study and long-term safety data (serious adverse events [SAEs] and AESIs) were pooled across the clinical trials. The safety of other recombinant nanoparticle vaccine antigens with Matrix-M adjuvant showed that each antigen and adjuvant regimen was acceptably well tolerated and resulted in safety profiles similar to those seen in the clinical trials of NVX-CoV2373 with Matrix-M adjuvant. In general, frequencies of solicited local and systemic TEAEs were increased in recipients who received Matrix-M-adjuvanted vaccines (compared to those who received vaccines without Matrix-M adjuvant) and in recipients who received two-dose regimens of Matrix-M-adjuvanted vaccine (compared to those who received one-dose regimens of Matrix-M-adjuvanted vaccine). Severe solicited TEAEs were reported in less than 10% of participants across the two-dose Matrix-M-adjuvanted vaccine groups and in less than 5% of participants across the one-dose Matrix-M-adjuvanted vaccine groups. Frequencies of unsolicited TEAEs were generally similar between the treatment groups and occurred in less than 10% of participants in 4 studies and in less than 30% of participants in Study RSV-E-205.

Pooled safety analyses of SAE and AESI data across the 5 trials showed no increased risks between the treatment groups across the two age strata evaluated (18 to 64 years and ≥ 65 years). Approximately 0.5% of participants in the Matrix-M-adjuvanted vaccine and active influenza comparator groups died, which was lower than the percentage of death (1.4%) in the placebo group. All deaths occurred in participants ≥ 65 years and none of the deaths were assessed as related to treatment. In participants 18 to 64 years of age, frequencies of other SAEs occurred at similar exposure-adjusted rates across the Matrix-M-adjuvanted vaccine (9.3 events per 100 subject years [SY]), Matrix-M-unadjuvanted vaccine (10.4 events per 100 SY), and active influenza vaccine comparator (13.1 events per 100 SY) groups, all of which had higher exposure-adjusted rates than placebo (0 events per 100 SY). Two SAEs (pericarditis and convulsion) were assessed by the investigator as related to study treatment, both of which occurred in the Without Matrix-M-adjuvanted vaccine group. In participants ≥ 65 years of age, frequencies of other SAEs also occurred at similar exposure adjusted rates across the Any Dose Matrix-M-adjuvanted vaccine (12.6 events per 100 SY), Without Matrix-M-adjuvanted vaccine (11.6 events per 100 SY), and Active Influenza Vaccine Comparator (9.8 events per 100 SY) groups, all of which had lower exposure-adjusted rates than Placebo (17.7 events per 100 SY). There were 4 SAEs (all seizure) reported as potential immune-mediated medical conditions (PIMMCs), with 2 events each occurring in each age strata. In participants 18 to 64 years of age, both seizure events (2.1 events per 100 SY) were reported in the Without Matrix-M-adjuvanted vaccine group; in participants ≥ 65 years of age, both seizure events were reported in the 50 μ g Matrix-M-adjuvanted vaccine group. All events occurred in participants with a prior history of seizure and/or additional risk factors for seizure occurrence.

In conclusion, both short- and long-term safety data from other recombinant nanoparticle vaccine antigens with Matrix-M adjuvant were acceptably well tolerated in healthy and medically stable participants 18 years of age and older. In the short-term, these safety profiles appear similar to those seen across clinical trials with SARS-CoV-2 rS with Matrix-M adjuvant. In the long-term, no increased risk was associated with any of the recombinant nanoparticle vaccine antigens with Matrix-M adjuvant supporting a favourable long-term safety profile of SARS-CoV-2 rS with Matrix-M adjuvant. It is concluded that the Matrix-M adjuvant does not pose any important safety concern.

Adverse Events of Special Interest

The Novavax list of AESIs is drawn from efforts by regulatory authorities, internationally recognised collaborations, and the scientific literature to identify AESIs for vaccinations, and COVID-19 vaccinations specifically. The list of AESIs is provided in Annex 7.

Risk of vaccine drop out

No specific treatment-related TEAEs led to study discontinuation in either the NVX-CoV2373 or placebo group.

Vaccine discontinuation due to TEAEs was very low in the NVX-CoV2373 group (n = 84 participants [0.3%]) in the pooled safety dataset (N = 30,058). This rate was similar to that in the placebo group (n = 43 participants [0.2%]) in the pooled safety dataset (N = 19,892).

In paediatric participants 12 to < 18 years of age, there were no TEAEs reported in either the NVX-CoV2373 or placebo group that led to study discontinuation in the 2019nCoV-301 paediatric expansion study.

Relevance of long-term follow-up

Given the expedited nature of the NVX-CoV2373 clinical development programme in response to the global COVID-19 pandemic, understanding of the long-term safety profile of NVX-CoV2373 is currently limited. Consequently, while there is no scientific evidence to suspect an adverse long-term safety profile, it is recognised that further follow-up for all vaccines developed in response to the COVID-19 pandemic is required.

In the ongoing clinical studies, it is planned to follow all participants contributing to safety pool for up to 6 months (505), 1 year post-vaccination (Studies 101 Part 1 and 2, 501, and 302) or 2 years post-vaccination (Study 301). However, it is recognised that with the increasing availability of alternative authorised COVID-19 vaccines, individuals may seek to receive confirmation of their vaccination status, thereby requesting to be unblinded and thus limiting the ability to collect long-term placebo-controlled follow-up data for the entire study population in an unbiased fashion.

Risks of vaccination errors in the context of mass vaccination campaigns

As Nuvaxovid may be administered in large-scale vaccination programmes, there may be a potential for vaccination errors. Vaccination errors may relate to administration, vaccination scheme, storage conditions, or errors associated with multidose vials. These potential vaccination errors are mitigated through a number of strategies:

- SmPC section 6.6 contains instructions on administration and storage conditions for Nuvaxovid. Instructions on vaccination scheme are provided in SmPC section 4.2.
- Medical information contact centers are available for the public and HCPs to respond to medical information inquiries about Nuvaxovid.
- A website (www.NovavaxCovidVaccine.com) is in place for more information.
- Vaccination reminder cards and stickers with batch/lot numbers are available to member states, if requested, for use by member state vaccinators.

Furthermore, as other COVID-19 vaccines are also available, there is the potential for confusion or interchangeability with other COVID-19 vaccines. The above mechanisms are in place to facilitate safe use and avoidance of vaccination errors.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risks

Myocarditis and/or pericarditis

Risk-benefit impact: Myocarditis and/or 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 risk-benefit balance of the vaccine is considered minimal. **Important Potential Risks**

Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)

Risk-benefit impact: Theoretically, vaccination against SARS-CoV-2 may be associated with enhanced severity of COVID-19 episodes, which would manifest as VAED. VAERD refers to the predominantly lower respiratory tract presentation of VAED. Although available data have not identified VAED/VAERD as a concern for NVX-CoV2373, the risk of VAED/VAERD cannot be ruled out. VAED/VAERD may be serious or life-threatening, and requires early detection, careful monitoring, and timely medical intervention.

Missing information

Use in pregnancy and while breastfeeding

Risk-benefit impact: 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

Risk-benefit impact: 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)

Risk-benefit impact: 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

Risk-benefit impact: 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

Risk-benefit impact: 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

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

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important identified risks

Table SVII.3.1.1: Myocarditis and/or Pericarditis

Important identified risk: Myocarditis and/or pericarditis	
Potential mechanism(s)	<p>Myocarditis can be caused by a variety of infectious and non-infectious causes, with viruses being the most common pathogen. Other common causes include autoimmune disorders such as systemic lupus erythematosus. In the general population, the incidence of myocarditis is approximately between 10 to 20 cases per 100,000 persons per year. According to some estimates, 1% to 5% of all patients with acute viral infections may involve the myocardium. The majority of patients are young, healthy males. Individuals who are most susceptible to myocarditis include children, pregnant women, and those who are immunocompromised (Kang and An 2021).</p> <p>Myocarditis begins with the direct invasion of an infectious agent and its subsequent replication within or around the myocardium causing myonecrosis. The subacute phase is defined by an increase in autoimmune-mediated injury with activated T cells and B cells and subsequent antibody production creating cardiac autoantibodies along with inflammatory proteins (Kang and An 2021).</p> <p>A mechanism of action by which a vaccine could cause myocarditis and/or pericarditis has not been established.</p>
Evidence source(s) and strength of evidence	Literature on COVID-19 vaccines, post-market safety data, and clinical trial data.

Table SVII.3.1.1: Myocarditis and/or Pericarditis

Important identified risk: Myocarditis and/or pericarditis	
Characterisation of risk	<p><u>Clinical trial experience</u></p> <p><i>Participants 12 years of age and older</i></p> <p>In the placebo-controlled safety dataset for NVX-CoV2373 (i.e., prior to blinded crossover), 30,058 subjects received active vaccine and 19,892 subjects received placebo. Two cases of myocarditis were reported following exposure to NVX-CoV2373 and one case was reported following exposure to placebo. The myocarditis/pericarditis exposure adjusted incidence rate per 100 person years (PY) of 0.03 events/100 PY for NVX-CoV2373 compared to 0.02 events/100 PY for placebo with an adjusted risk difference of 0.00 (95%: -0.06, 0.07). In the post-crossover phase of the studies 301 and 302, three cases of myocarditis were reported. The observed rate of 3 cases/14,513 PY falls within the expected rate of 1.6-4.6 cases/14,513 PY as determined by the EU ACCESS study. Of note, the exposure adjusted incidence post-crossover is the same as the placebo incidence of 0.02 events/100 person years during the placebo-controlled period suggesting a stable background incidence rate.</p> <p>The Sponsor assessed the causality as not related for the five cases occurring after exposure to NVX-CoV2373; all cases were attributed to alternative aetiologies, including reasonable infectious and/or non-infectious causes. There were no cases of myocarditis/pericarditis assessed as related by the Sponsor.</p> <p>Review of data from the placebo-controlled data set of the 2019-nCoV-301 Paediatric Expansion study in participants 12 to <18 years of age demonstrated no cases of myocarditis or pericarditis.</p> <p><u>Post-marketing experience</u></p> <p>A broad search strategy of post-marketing data using SMQ (broad) non-infectious myocarditis/pericarditis and HLTs infectious myocarditis, infectious pericarditis, non-infectious myocarditis, and non-infectious pericarditis retrieved 98 cases of myocarditis and/or pericarditis cumulatively as of 15 November 2022. All reports retrieved by the broad search strategy were adjudicated against the Brighton Collaboration (BC) case definitions for myocarditis and pericarditis, and the cases that met BC levels 1-3 criteria (n=38) are further described here. Cases were equally distributed in male and female adults with most (n=11, male and female inclusive) occurring in those 30-39 years of age. In the 29 cases where time to onset was described, 19 events occurred within 0-7 days of vaccination. Event outcomes in the initial case reports were as follows: Unknown: 18, Recovered/Resolved: 7, Recovered with Sequelae: 1, Recovering/Resolving: 12, Not Recovered/Not Resolved: 27, Fatal: 0. Twenty nine of 38 cases met the case seriousness criteria of Medically Significant. A disproportionate number of cases, 24 (63.2%), were reported from Australia where active surveillance programmes are in place. Risk characterisation will continue to be evaluated as post-marketing data is received.</p>
Risk factors and risk groups	Adolescent and young adult males following the second dose of vaccine may be at higher risk (Gargano 2021). Immunocompromised patients may be at a higher risk.
Preventability	Routine risk minimisation measures in the form of product labelling are included in the EU SmPC.
Impact on the risk-benefit balance of the product	Balanced with the risk of death and illness (including myocarditis) seen with COVID-19 itself, the vaccine has a favourable risk-benefit balance.
Public health impact	As this event is limited to the individual patient and considering the low rates of myocarditis and/or pericarditis reported following vaccination, balanced with the risk of death and illness (including myocarditis) caused by COVID-19, the public health impact is considered minimal.

Important potential risks

Table SVII.3.1.2: Vaccine-Associated Enhanced Disease (VAED), Including Vaccine-Associated Enhanced Respiratory Disease (VAERD)

Important potential risk: Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)	
Potential mechanism(s)	The pathogenesis of VAED in the context of SARS-CoV-2 is unclear, and there are no consistent mechanisms or immune markers of disease enhancement from non-clinical studies. Although animal models of SARS-CoV-2 infection may elucidate mechanisms of immune protection, we need observations of enhanced disease in individuals who receive COVID-19 vaccines to understand the risk of immune enhancement of disease (Haynes 2020). VAERD refers to the predominantly lower respiratory tract presentation of VAED. The mechanism of the pathogenesis of VAERD may be specific to the lower respiratory tract or may be part of a systemic process. The vaccine induces a Th1-biased immune response, which is considered less likely to be associated with VAED. Less severe cases of SARS were associated with accelerated induction of a Th1 cell response; whereas, Th2 cell responses have been associated with enhancement of lung disease following infection in hosts parenterally vaccinated with inactivated SARS-CoV vaccines (Lambert 2020).
Evidence source(s) and strength of evidence	Literature on viral vaccines, safety information of other SARS-CoV-2 vaccines, clinical trials. VAED has been rarely encountered with existing vaccines or viral infections. It was observed in children given formalin-inactivated whole-virus vaccines against RSV and measles virus (Haynes 2020). No events of VAED/VAERD have been reported in the current NVX-CoV2373 clinical development programme. There is a theoretical concern that vaccination against SARS-CoV-2 may be associated with enhanced severity of COVID-19 episodes, which would manifest as VAED/VAERD (Graham 2020; Munoz 2021).
Characterisation of risk	VAED/VAERD, if it would occur in vaccinated persons, would manifest as a modified and/or more severe clinical presentation of SARS-CoV-2 viral infection upon subsequent natural infection. This may result in individuals assumed to be at lower risk for severe COVID-19 having more severe disease, for individuals at known risk for severe COVID-19 (e.g., older or immunocompromised, immunocompromised children, and children with chronic conditions) having higher rates of fatal outcomes, or for observation of an unfavourable imbalance in severe COVID-19 cases in vaccinated individuals when compared to those not vaccinated. <u>Clinical trial experience</u> <i>Participants 18 years of age and older</i> No events of VAED/VAERD have been reported in adult participants in the current NVX-CoV2373 clinical development programme and in fact the vaccine has been shown to prevent severe illness. <i>Participants 12 to < 18 years of age</i> Data from 2019-nCoV-301 Paediatric Expansion study in paediatric participants 12 to < 18 years of age demonstrated no cases of VAED/VAERD. <u>Post-marketing experience</u> As of 15 November 2022, there were no cases reported of VAED (including VAERD) according to the prescribed search strategy (PTs: Vaccine-associated enhanced disease; Vaccine-associated respiratory disease).
Risk factors and risk groups	There are no known risk factors or specific risk populations identified for VAED/VAERD. The demonstration of some disease enhancement with any candidate vaccine after viral challenge in animal models should not necessarily represent a no-go signal for deciding whether to progress into early trials in clinical development of a COVID-19 vaccine (Lambert 2020). Population-based surveillance might give more insight in this, should any VAED occur.

Table SVII.3.1.2: Vaccine-Associated Enhanced Disease (VAED), Including Vaccine-Associated Enhanced Respiratory Disease (VAERD)

Important potential risk: Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)	
Preventability	Prevention of VAED/VAERD in the context of SARS-COV-2 is currently unknown. Population-based surveillance might give more insight in this, should any VAED occur.
Impact on the risk-benefit balance of the product	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. However, as no cases have been reported, there is no impact on the benefit-risk balance.
Public health impact	As this safety concern is currently theoretical and has not been observed in the completed/ongoing trials or in the post-marketing setting in relation to NVX-CoV2373/Nuvaxovid administration, there is no public health impact at this time.

SVII.3.2. Presentation of the missing information

Table SVII.3.2.1: Use in Pregnancy and While Breastfeeding

Evidence Source	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.
Population in need of further characterisation	Pregnant and breastfeeding women.
Anticipated risk/consequence of the missing information	Targeted populations of the indication will include women of childbearing potential, thus, vaccination of pregnant and/or breastfeeding women will occur.

Table SVII.3.2.2: Use in Immunocompromised Patients

Evidence Source	The vaccine has not been studied in individuals with immunocompromised conditions, except for subjects with HIV. Subjects with HIV were not excluded from the clinical programme, and 244 participants were enrolled in the 2019nCoV-501 study. The safety profile of NVX-CoV2373 in HIV-positive participants in this study was similar to that seen in HIV-negative participants. There is no evidence that the safety profile of this population receiving NVX-CoV2373 will be different to that of the general population, but given the paucity of data, the possibility cannot be excluded.
Population in need of further characterisation	Individuals with compromised immune function due to acquired or genetic conditions or conditions requiring the use of immunosuppressants.
Anticipated risk/consequence of the missing information	Vaccines may be less effective in severely immunocompromised patients, as the vaccinees weakened immune system may not mount a sufficient response.

Table SVII.3.2.3: Use in Frail Patients with Comorbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)

Evidence Source	The vaccine has not been studied in frail (unstable) individuals with severe comorbidities that may compromise immune function due to the condition or treatment of the condition. Frail patients with comorbidities (e.g., COPD, DM, chronic neurological disease, cardiovascular disorders) are potentially at risk of developing a more severe manifestation of COVID-19. There is no evidence that the safety profile of this population receiving NVX-CoV2373 will be different to that of the general population, but given the paucity of data, the possibility cannot be excluded.
Population in need of further characterisation	Frail individuals with comorbidities (e.g., COPD, DM, chronic neurological disease, cardiovascular disorders).
Anticipated risk/consequence of the missing information	Frail individuals with unstable and/or severe health conditions and comorbidities may experience a different outcome of the vaccination than that achieved in generally healthy individuals administered vaccines.

Table SVII.3.2.4: Use in Patients with Autoimmune or Inflammatory Disorders

Evidence Source	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.
Population in need of further characterisation	Patients with autoimmune or inflammatory disorders.
Anticipated risk/consequence of the missing information	Individuals with autoimmune or inflammatory disorders may experience a different outcome than achieved in healthy individuals administered vaccines.

Table SVII.3.2.5: Interaction with Other Vaccines

Evidence Source	There is limited information on the safety of the vaccine when administered with other vaccines within 28 days prior to the first dose or any dose of NVX-CoV2373, except for seasonal influenza vaccine, < 14 days. Approximately 400 participants were concomitantly administered a seasonal influenza vaccine with NVX-CoV2373 or placebo. 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.
Population in need of further characterisation	Individuals who will receive other vaccines within 28 days prior to or 14 days after immunisation with NVX-CoV2373/Nuvaxovid.
Anticipated risk/consequence of the missing information	Theoretically, vaccines may interact with each other and change the immune response to either vaccine or induce safety concerns.

Table SVII.3.2.6: Long-Term Safety

Evidence Source	Understanding of the long-term safety profile of NVX-CoV2373 is currently limited. The median duration of safety follow-up in each of the two Phase 3 studies was at least 60 days. The maximum follow-up post dose 2 will be 24 months.
Population in need of further characterisation	Individuals receiving NVX-CoV2373/Nuvaxovid.
Anticipated risk/consequence of the missing information	There are no known risks with a potentially delayed onset, with the exception of the theoretical concern of VAED/VAERD. Whilst there is currently no evidence to suspect an adverse long-term safety profile, given the paucity of data, the possibility cannot be excluded.

Part II: Module SVIII – Summary of the safety concerns

Table SVIII.1: Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	Myocarditis and/or pericarditis
Important potential risks	Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)
Missing information	<ul style="list-style-type: none"> Use in pregnancy and while breastfeeding Use in immunocompromised patients Use in frail patients with comorbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders Interaction with other vaccines Long-term safety

Part III: Pharmacovigilance Plan (Section including Post-authorisation Safety Studies)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance (PV) activities are consistent with the EMA Guidelines on Good Pharmacovigilance Practices (GVP) in general and for COVID-19 vaccines.

Routine PV activities for the lifecycle of a product are critical components to the detection, assessment, and understanding of risks. Activities include the continuous collection, review and processing of individual case safety reports, signal detection and management, and the reporting of individual case safety reports and aggregate safety reports to health authorities.

A comprehensive description of all aspects of the PV system is provided in the Pharmacovigilance System Master File (PSMF), which is available upon request.

Novavax monitors the safety profile of its products, evaluates issues potentially impacting product benefit-risk profiles in a timely manner, and ensures that appropriate communication of relevant safety information is conveyed in a timely manner to regulatory authorities, other interested parties as appropriate, and in accordance with international principles and prevailing regulations.

Signal detection activities

Surveillance is conducted for Nuvaxovid according to EMA Consideration on core requirements for RMPs of COVID-19 vaccines, EMA GVP Module IX, Guideline on good pharmacovigilance practices (GVP) Product- or Population-Specific Considerations I: Vaccines for prophylaxis against infectious diseases, and the Nuvaxovid post-authorization surveillance plan.

Routine pharmacovigilance surveillance and signal detection activities involve both qualitative and quantitative methods performed weekly. Data sources include the Novavax global safety database, medical literature, EVDAS and VAERS and information from health authorities. Qualitative methods include individual case medical review during and after case processing and line-listing medical reviews of both serious and nonserious ICSRs by Novavax medical safety directors. Quantitative methods include interval and cumulative review of data across different strata including Adverse Events of Special Interest, designated medical events (DMEs)/important medical events (IMEs), MedDRA HLTs, SMQs (broad and narrow) and trend analyses across MedDRA PTs. Safety observations that are identified for possible validation undergo a preliminary review, and, if validated, a complete evaluation is performed.

Adverse events of special interest have been identified prospectively for close monitoring. These potential adverse reactions following immunization undergo observed-to-expected analyses as an additional signal generation methodology. Signals that reach statistical significance are validated and prioritized for complete evaluation of available data, including adjudication against an established case definition if available. Results, interpretation, and related actions (if warranted) are provided in Summary Safety Reports.

Summary Safety Reports (SSRs)

SSRs have been implemented for the pandemic setting according to the framework and specified content established in the guidance document EMA Consideration on core requirements for RMPs of COVID-19 vaccines and other relevant health authority requirements. SSRs are currently submitted bi-monthly. The topics covered in SSRs include:

- 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 rather than distributed doses whenever possible, stratified by region (and within the EU also by country), by age groups, gender, by dose number (when applicable)
- Safety-related changes to the reference safety information and actions taken in the interval for safety reasons
- List of ongoing and closed validated 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 SSR
- Summaries of reported cases of all AESIs and RMP safety concerns: report numbers and cases, including cumulative O/E analysis (when possible)

- Discussion of an unusual pattern of fatal reports, if observed, including numbers and relevant cases (considering co-morbidities and frailty) and 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
- Risk/benefit considerations

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 traces 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, contains the product global trade identification number (GTIN), lot/batch number, and expiry date printed as human readable information and a scannable GS1 1D Data Matrix code.

Further, vaccination reminder cards are available (Annex 7) 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 or other doses 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;
- Placeholder space for a third/"other" dose of the vaccine;
- Novavax website and QR code that links to [NovavaxCovidVaccine.com](https://www.novavax.com/covid-vaccine); 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 are provided to support documentation of the batch/lot traceability on the vaccination reminder card and for use in the vaccinee's medical records. Novavax acknowledges that some EU member states may require utilisation of nationally mandated vaccination cards or electronic systems to document batch/lot number; therefore, the available vaccination reminder cards and/or stickers with printed lot/batch information may not be utilised in all member states.

Routine PV activities beyond AE reporting and signal detection:

Specific adverse reaction follow-up forms for the following safety concerns:

- Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)
- Myocarditis and/or pericarditis

Please find examples of these questionnaires in [Annex 4](#).

III.2 Additional Pharmacovigilance Activities

Continuation of safety surveillance from ongoing clinical trials is a priority and included as an additional PV activity, as ongoing data collection in these studies is also anticipated to provide further data to characterise the NVX-CoV2373 safety profile. These studies are not considered post-authorisation safety studies (PASS); however, they are included in this RMP as additional PV activities in accordance with EMA Consideration on core requirements for RMPs of COVID-19 vaccines.

Clinical trials

Study short name and title: 2019nCoV-101; A 2-part, Phase 1/2, Randomized, Observer-Blinded Study to Evaluate the Safety and Immunogenicity of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine (SARS-CoV-2 rS) With or Without Matrix-M Adjuvant in Healthy Subjects

Rationale and study objectives: The primary objective for Part 1 of this study is to evaluate the safety and immunogenicity of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine (SARS-CoV-2 rS) with or without Matrix-M adjuvant in healthy subjects.

The primary objectives for Part 2 of this study are 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), to identify dose(s) to potentially take forward in an emergency use authorisation (EUA) setting and/or for Phase 3 efficacy or effectiveness trial(s), and to evaluate the safety and immunogenicity of booster doses of NVX-CoV2373 administered approximately 6 to 12 months after the primary vaccination series.

Study design: A 2-part, phase 1/2, randomized, observer-blinded study

Study population: Healthy adult patients 18 – 59 years of age (Part 1). Healthy adult patients 18–84 years of age (Part 2).

Milestones: Study 2019nCoV-101 (Part 1) was initiated on 25 May 2020 with the first patient enrolled on 06 June 2020. Interim clinical study report (CSR): 25 February 2021. Final CSR for 2019nCoV-101 (Part 1) submission: 25 March 2022.

Study 2019nCoV-101 (Part 2) was initiated on 24 August 2020 (first participant screened) and completed enrollment on 25 September 2020. The data cutoff date of the Day 35 interim analysis was 09 December 2020. The study remains ongoing through approximately 1 year follow-up from the Day 21 injection. A booster dose was added at 6 months and 1 year for some subjects; as a result some subjects will remain in the study for an additional 6 months following their last injection. Interim CSR for 2019nCoV-101 (Part 2) submission: 13 April 2022.

Final CSR estimated date: 31 December 2023.

Study short name and title: **2019nCoV-501; A Phase 2a/b, Randomized, Observer-Blinded, Placebo-Controlled Study to Evaluate the Efficacy, Immunogenicity, and Safety of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine (SARS-CoV-2 rS) With Matrix-M Adjuvant in South African Adult Subjects Living Without HIV; and Safety and Immunogenicity in Adults Living With HIV**

Rationale and study objectives: The primary objective of Study 2019nCoV-501 is to evaluate the efficacy, immunogenicity, and safety of a SARS-CoV-2 rS with Matrix-M adjuvant in South African adult subjects living with human immunodeficiency virus (HIV); and safety and immunogenicity in adults living with HIV.

Study design: A Phase 2a/b, randomized, observer-blinded, placebo-controlled trial

Study population: Adult HIV-negative or HIV-positive participants in South Africa. Eligible HIV-negative participants were healthy males and nonpregnant females, ≥ 18 to < 85 years of age, with a BMI of 17-40 kg/m² and a documented HIV-negative test result by HIV test assay approved in South Africa.

Milestones: Study 2019nCoV-501 was initiated on 17 August 2020 (first participant screened) and completed enrollment into the initial phase on 25 November 2020. A booster dose was added at 6 months in the subjects who received the active vaccine in the initial vaccination series. Interim CSR: 13 April 2022. Final CSR estimated date: 31 March 2023.

Study short name and title: **2019nCoV-302; A Phase3, Randomised, Observer-Blinded, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine (SARS-CoV-2 rS) with Matrix-M adjuvant in Adult Participants 18-84 Years of Age in the United Kingdom**

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

The exploratory objective of the Seasonal Influenza Vaccine Substudy in Study 2019nCoV-302 is to evaluate the safety and immunogenicity of SARS-CoV-2rS with Matrix-M adjuvant in the initial set of vaccinations when co-administered with a licensed seasonal influenza vaccine.

Study design: Phase 3, Randomised, Observer-Blinded, Placebo-Controlled Trial

Study population: Adult patients 18 – 84 years of age in the UK.

Milestones: This study was initiated on 28 September 2020 (first participant screened) and completed enrollment on 28 November 2020 at 33 sites across the UK. Interim CSR: 06 May 2021. Final CSR estimated date: 31 March 2023.

Study short name and title: **2019nCoV-505; A Phase 2 Study of the Safety and Immunogenicity of a COVID-19 Vaccine in People Living with HIV (PLWH)**

Rationale and study objectives:

1. To describe the amplitude, kinetics, and durability of immune response to NVX-CoV2373 in terms of Enzyme Linked Immunosorbent Assay (ELISA) units of serum IgG antibodies, titers of neutralizing antibody, and titers of human angiotensin-converting enzyme 2 (hACE2) receptor binding inhibition activity assayed in a system using the SARS-CoV-2 rS protein(s) (reflecting the amino acid sequence of that of the prototype virus) at selected time points, stratified by baseline HIV status and in PLWH, stratified by level of control of HIV infection into well-controlled and less well-controlled treatment groups. To include reverse cumulative distribution curves.
2. To assess overall safety through Day 84 after initial vaccination for all unsolicited AEs and all medically attended adverse events (MAAEs); and safety through Days 120 and 180 (EoS) following vaccination for any MAAE attributed to vaccine, AESIs, or serious adverse events.
3. To accumulate and describe the safety experience for NVX-CoV2373 based on solicited short-term reactogenicity (by toxicity grade) and by AE profile for vaccination through Day 84 in PLWH and HIV-negative adult participants and, in PLWH, stratified by level of control of HIV infection into well-controlled and less-well-controlled treatment groups.

Study design: A Phase 2, randomized, observer-blinded study

Study population: PLWH and HIV-negative adults 18 to 65 years of age, inclusive.

Milestones: Final CSR estimated date: 30 November 2023.

Study short name and title: **2019nCoV-301; A phase 3, Randomized, Observer-Blinded, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Immunogenicity of a SARS-COV-2 Recombinant Spike Protein Nanoparticle Vaccine (SARS-COV-2 rS) with Matrix-M Adjuvant in Adult Participants ≥ 18 years with a Pediatric Expansion in Adolescents (12 to < 18 years)**

Rationale and study objectives: The primary objectives of 2019nCoV-301 are: To evaluate the efficacy of a two-dose regimen of SARS-CoV-2 rS adjuvanted with Matrix-M compared to placebo against 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. Evaluate the efficacy and safety after vaccination with SARS-CoV-2 rS adjuvanted with Matrix-M compared to placebo in paediatric participants 12 to < 18 years of age. Evaluate the safety and immunogenicity following a single

booster dose approximately 6 months following active vaccination in adults and adolescents. Evaluate the safety and immunogenicity following a second booster dose approximately 6 months following the first booster vaccination in a sub-study of adults enrolled in the study.

Study design: A Phase 3, Randomized, Observer-Blinded, Placebo-Controlled Study

Study population: Adult participants ≥ 18 years of age who, by virtue of age, race, ethnicity or life circumstances were considered at substantial risk of exposure to and infection with SARS-CoV-2. Eligible participants were medically stable and had no history of previous laboratory-confirmed (by PCR or serology to SARS-CoV-2) diagnosis of SARS-CoV-2 infection or COVID-19 prior to randomisation. Paediatric participants 12 to < 18 years of age were included in the 2019nCoV-301 paediatric expansion study and included in subsequent protocol amendments as applicable.

Milestones: Interim CSR: 09 Aug 2021. Final CSR estimated date: 31 December 2023. Submission of the interim CSR for 2019nCoV-301 pediatric expansion study to EMA: 08 March 2022.

Study short name and title: **2019nCoV-311; A phase 3 Boosting Study for the SARS-CoV-2 rS Vaccine**

Rationale and study objectives: To evaluate the safety and immunogenicity of 2 booster doses of the monovalent prototype vaccine (NVX-CoV2373), monovalent Omicron subvariant vaccines (NVX-CoV2515 [BA.1] and NVX-CoV2540 [BA.5]) and bivalent vaccines (NVX-CoV2373 + NVX-CoV2515 and NVX-CoV2373 + NVX-CoV2540) in participants who have already been immunized with 2 or 3 doses of the Moderna or Pfizer/BioNTech prototype vaccines. Additionally, the study will investigate the ability of the NVX-CoV2515 vaccine to demonstrate a statistically superior difference in the titers of cross-neutralizing antibodies and IgG antibodies compared to the NVX-CoV2373 prototype vaccine.

Study design: Phase 3, Randomised, Observer Blinded Study

Study population: Medically stable male and nonpregnant females ≥ 18 and ≤ 64 years of age in Australia who have previously received 2 doses of the Moderna and/or Pfizer/BioNTech prototype vaccines ≥ 180 days or 3 doses of the Moderna or Pfizer/BioNTech prototype vaccines ≥ 90 days prior to study vaccination.

Milestones: Final CSR estimated date: 31 March 2024.

Post-authorisation studies

To further characterise the Nuvaxovid safety and effectiveness profile, the following five (5) non-interventional studies will be conducted:

Study short name and title: **2019nCoV-402 (UK Post-Authorisation Safety Study Using the Clinical Practice Research Datalink (CPRD))**

Rationale and study objectives: A surveillance study to characterise the safety profile of Nuvaxovid in adults aged 12 years and older in the real-world setting using the Clinical Practice Research Datalink (CPRD) Aurum database.

Objective: To evaluate the risk of select safety outcomes of interest following vaccination with the Nuvaxovid using a (i) a self-controlled case series (SCCS) design and (ii) a comparative cohort study design.

Study design: Two methods are planned for this study to assess the risk of select AESIs: 1) a SCCS to compare the incidence for AESIs within a pre-specified risk window following Nuvaxovid vaccination with incidence during time following the vaccination within the same individual, and 2) a retrospective cohort study design comparing Nuvaxovid vaccinated individuals with Pfizer-BioNTech-vaccinated, Moderna-vaccinated and unvaccinated individuals. The risk window for each acute AESI will be defined in the study protocol.

Study population: The source population will comprise all individuals registered in CPRD Aurum (and linked databases) from the first date of Nuvaxovid administration in the real-world setting, following receipt of regulatory authorisation in the UK.

Milestones: The draft study protocol was submitted on 31 March 2022. A revised protocol was submitted on 30 September 2022 and another is planned by 31 March 2023.

Two interim reports are planned for submission by 30 June 2023 and 30 June 2024. A final study report is planned for submission by 30 June 2025.

Study short name and title: **2019nCoV-405 (Global Pregnancy and infant outcomes study using the COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER))**

Rationale and study objectives: To estimate the risk of obstetric outcomes and infant outcomes among pregnant women exposed to a single (homologous) or mixed (heterologous) Nuvaxovid series from 30 days prior to the first day of the last menstrual period (LMP) to end of pregnancy and their offspring relative to a matched reference group who received no COVID-19 vaccinees during pregnancy.

Study design: A registry-based observational cohort safety study.

Study population: The source population will comprise of pregnant women who are aged 18 to 49 years old (and infants born to them).

Milestones: The draft study protocol was submitted on 30 March 2022.

Interim reports are planned for submission by 30 June 2023, 30 June 2024, 30 June 2025, and 30 June 2026. A final study report is planned for submission by 30 June 2027.

Study short name and title: **2019nCoV-404 (US Post-authorization safety study using a claims and/or EHR (Electronic Health Record) database)**

Rationale and study objectives: To evaluate the risk of select AESIs following vaccination with at least one dose of the Novavax COVID-19 Vaccine, Adjuvanted in the US .

Study design: Two methods are planned for this study to assess the risk of select AESIs: 1) a SCCS to compare the incidence for the select acute AESIs within a pre-specified risk window following vaccination with the Novavax COVID-19 Vaccine, Adjuvanted with incidence during all other times following the vaccination within the same individual, and 2) a retrospective cohort study design with unvaccinated and recipients of mRNA COVID-19 vaccines as reference groups.

Study population: The source population will comprise health plan members in the selected insurance claims database and/or electronic health record (EHR) database (to be determined) during the study period from the first date of Novavax COVID-19 Vaccine, Adjuvanted administration in the real-world setting, following receipt of regulatory authorisation in the US, through approximately 30 months afterward.

Milestones: The draft study protocol was submitted to EMA on 29 June 2022. A revised protocol was submitted on 28 November 2022.

Two interim reports are planned for submission by 30 September 2023 and 30 September 2024. A final study report is planned for submission by 30 September 2025.

Study short name and title: 2019nCoV-401 (EU/EEA Post-authorisation effectiveness study based on a test-negative design using the COVIDRIVE platform)

Rationale and Study Primary Objectives:

1. To estimate COVID-19 vaccine effectiveness (CVE) of Nuvaxovid against hospitalisation due to laboratory-confirmed SARS-CoV-2 in severe acute respiratory infection (SARI) patients who have completed their primary vaccination series, compared to unvaccinated patients.
2. To estimate CVE of Nuvaxovid against hospitalisation due to laboratory-confirmed SARS-CoV-2 in SARI patients who previously completed at least a primary series with any COVID-19 vaccine compared to a) unvaccinated patients and b) patients who previously completed at least a primary series with any COVID-19 vaccine but did not receive the last additional dose.
3. To estimate CVE across brands against hospitalisation due to laboratory-confirmed SARS-CoV-2 in SARI patients who previously completed at least a primary series with any COVID-19 vaccine but who did not receive the last additional dose, compared to unvaccinated patients.

For the above objectives, to estimate Nuvaxovid effectiveness against COVID-19 hospitalisations stratified by SARS-CoV-2 variants to the extent such data are available.

Study design: A 2-year observational, multi-country, prospective, hospital-based case-control study using a test-negative design (TND).

Study population: Adult patients aged 18 years and older admitted to the hospital, through the Emergency Department or transferred from other hospitals or health facilities, fulfilling the case definition for COVID-19 including clinical criteria (e.g., cough, fever, SOB, sudden onset of anosmia, ageusia, or dysgeusia), diagnostic imaging criteria, and/or epidemiological criteria.

COVIDRIVE currently has sites in 11 different European countries including the UK. Site selection for this study will depend on Nuvaxovid uptake in each country. The COVIDRIVE study was expected to start in July 2021 (by other vaccine manufacturers) and there is a plan to gradually expand the number of sites/countries as new COVID-19 vaccines enter the market.

Milestones: The draft study protocol was submitted to EMA on 28 April 2022 and a revised protocol on 30 August 2022.

Interim reports are planned for submission by 31 July 2023, 31 January 2024, and 31 July 2024. The first progress report submission was 30 January 2023. A final study report is planned for submission by 31 January 2025.

Study short name and title: 2019nCoV-403 (US Post-authorization effectiveness study using a claims and/or EHR database)

Rationale and Study Objectives:

1. Primary objective: to estimate the effectiveness of the Novavax COVID-19 Vaccine, Adjuvanted in preventing COVID-19 hospitalisations.
2. Secondary objectives:
 - a. To estimate the effectiveness of the Novavax COVID-19 Vaccine, Adjuvanted in reducing clinically defined laboratory-confirmed severe SARS-CoV-2 infection (i.e., cases that resulted in hospitalisation, admission to the ICU, and/or death)
 - b. To assess the effectiveness of the Novavax COVID-19 Vaccine, Adjuvanted:
 - i. after a single dose in reducing clinically defined SARS-CoV-2 infection
 - ii. against SARS-CoV-2 variants (where data is available)
 - iii. by subgroups defined by age, sex, race/ethnicity, comorbidities/coinfections, prior SARS-CoV-2 infection, concomitant vaccinations, concomitant medications, and/or other characteristics

Study design: This is a retrospective cohort study.

Study population: The source population will comprise health plan members in the selected insurance claims database and/or EHR database (to be determined) during the study period from the first date of administration of the Novavax COVID-19 Vaccine, Adjuvanted in the real-world setting, following receipt of regulatory authorisation in the US, through approximately 30 months afterward.

Milestones: The draft study protocol was submitted on 29 June 2022 following receipt of regulatory authorisation in the US. The revised protocol was submitted on 29 November 2022.

Two interim reports are planned for submission by 30 September 2023 and 30 September 2024. A final study report is planned for submission by 30 September 2025.

III.3 Summary Table of Additional Pharmacovigilance Activities

Table Part III.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				
2019nCoV-101 (Part 2) Ongoing	<ul style="list-style-type: none"> 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). Evaluate the safety and immunogenicity of booster doses of NVX-CoV2373 administered approximately 6 and 12 months after the primary vaccination series. 	Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) Myocarditis and/or pericarditis Long-term safety	Final CSR	31 December 2023
2019nCoV-501 Ongoing	To evaluate the efficacy, immunogenicity, and safety of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine (SARS-CoV-2 rS) with Matrix-M adjuvant in South African adult subjects living without HIV; and safety and immunogenicity in adults living with HIV.	Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) Myocarditis and/or pericarditis Use in immunocompromised patients Long-term safety	Final CSR	31 March 2023

Table Part III.1: Ongoing and Planned Additional Pharmacovigilance Activities

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
<p>2019nCoV-302 Ongoing</p>	<ul style="list-style-type: none"> • Primary objective: To demonstrate the efficacy of SARS-CoV-2rS with Matrix-M adjuvant in the prevention of virologically confirmed (by polymerase chain reaction (PCR) to SARS-CoV-2), symptomatic COVID-19, when given as a two-dose vaccination regimen, as compared to placebo, in serologically negative (to SARS-CoV-2) adults. • Exploratory objective: To evaluate the safety and immunogenicity of SARS-CoV-2rS with Matrix-M adjuvant in the initial set of vaccinations when co-administered with a licensed seasonal influenza vaccine. 	<p>Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) Myocarditis and/or pericarditis Use in immunocompromised patients Interaction with other vaccines Long-term safety</p>	<p>Final CSR</p>	<p>31 March 2023</p>
<p>2019nCoV-505 Ongoing</p>	<ul style="list-style-type: none"> • To describe the amplitude, kinetics, and durability of immune response to NVX-CoV2373 in terms of ELISA units of serum IgG antibodies, titers of neutralizing antibody, and titers of human angiotensin-converting enzyme 2 (hACE2) receptor binding inhibition activity assayed in a system using the SARS-CoV-2 rS protein(s) (reflecting the amino acid sequence of that of the prototype virus) at selected time points, stratified by baseline HIV status and in PLWH, stratified by level of control of HIV infection into well-controlled and less well-controlled treatment groups. To include reverse cumulative distribution curves. • To assess overall safety through Day 84 after initial vaccination for all unsolicited AEs and all medically attended adverse events (MAAEs); and safety through Days 120 and 180 (EoS) following vaccination for any MAAE attributed to vaccine, AESIs, or serious adverse events. • To accumulate and describe the safety experience for NVX-CoV2373 based on solicited short-term reactogenicity (by toxicity grade) and by AE profile for vaccination through Day 84 in PLWH and HIV-negative adult participants and, in PLWH, stratified by level of control of HIV infection into well-controlled and less-well-controlled treatment groups. 	<p>Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) Myocarditis and/or pericarditis Use in immunocompromised patients</p>	<p>Final CSR</p>	<p>30 November 2023</p>

Table Part III.1: Ongoing and Planned Additional Pharmacovigilance Activities

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
<p>2019nCoV-311 Ongoing</p>	<p>To evaluate the safety and immunogenicity of 2 booster doses of the monovalent prototype vaccine (NVX-CoV2373), monovalent Omicron subvariant vaccines (NVX-CoV2515 [BA.1] and NVX-CoV2540 [BA.5]) and bivalent vaccines (NVX-CoV2373 + NVX-CoV2515 and NVX-CoV2373 + NVX-CoV2540) in participants who have already been immunized with 2 or 3 doses of the Moderna or Pfizer/BioNTech prototype vaccines and the ability of the NVX-CoV2515 vaccine to demonstrate a statistically superior difference in the titers of cross-neutralizing antibodies and IgG antibodies compared to the NVX-CoV2373 prototype vaccine.</p>	<p>Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) Myocarditis and/or pericarditis Long-term safety</p>	<p>Final CSR</p>	<p>31 March 2024</p>
<p>2019nCoV-301 Ongoing</p>	<ul style="list-style-type: none"> • To evaluate the efficacy of a two-dose regimen of SARS-CoV-2 rS adjuvanted with Matrix-M compared to placebo against 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. • Evaluate the efficacy and safety after vaccination with SARS-CoV-2 rS adjuvanted with Matrix-M compared to placebo in paediatric participants 12 to < 18 years of age. • Evaluate the safety and immunogenicity following a single booster dose approximately 6 months following active vaccination in adults and adolescents • Evaluate the safety and immunogenicity following a second booster dose approximately 6 months following the first booster vaccination in a sub-study of adults enrolled in the study 	<p>Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) Myocarditis and/or pericarditis Use in immunocompromised patients Use in patients with autoimmune or inflammatory disorders Long-term safety</p>	<p>Final CSR</p>	<p>31 December 2023</p>

Table Part III.1: Ongoing and Planned Additional Pharmacovigilance Activities

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
<p>2019nCoV-402 Post-Authorisation Safety Study Using the Clinical Practice Research Datalink (CPRD) Planned</p>	<p>To evaluate the risk of select safety outcomes of interest following vaccination with the Nuvaxovid using a (i) a self-controlled case series (SCCS) design and (ii) a comparative cohort study design.</p>	<p>Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) Myocarditis and/or 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</p>	<p>Interim reports Final study report</p>	<p>30 June 2023 and 30 June 2024 30 June 2025</p>
<p>2019nCoV-405 Global Pregnancy and infant outcomes study using the COVID-19 Vaccines International Pregnancy Exposure Registry Ongoing</p>	<p>To estimate the risk of obstetric outcomes, neonatal outcomes, and infant outcomes among pregnant women exposed to single (homologous) or mixed (heterologous) Nuvaxovid vaccine series from 30 days prior to the first day of the last menstrual period (LMP) to end of pregnancy and their offspring relative to a matched reference group who received no COVID-19 vaccines during pregnancy.</p>	<p>Use in pregnancy and while breastfeeding</p>	<p>Interim reports Final study report</p>	<p>30 June 2023, 30 June 2024, 30 June 2025, 30 June 2026 30 June 2027</p>

Table Part III.1: Ongoing and Planned Additional Pharmacovigilance Activities

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
<p>2019nCoV-404</p> <p>US Post-authorization safety study using a claims and/or EHR database</p> <p>Planned</p>	<p>To evaluate the risk of select AESIs following vaccination with at least one dose of the Novavax COVID-19 Vaccine, Adjuvanted using SCCS and cohort study designs.</p>	<p>Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)</p> <p>Myocarditis and/or pericarditis</p> <p>Use in immunocompromised patients</p> <p>Use in frail patients with co-morbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)</p> <p>Use in patients with autoimmune or inflammatory disorders</p> <p>Interaction with other vaccines</p> <p>Long-term safety</p>	<p>Interim reports</p> <hr/> <p>Final study report</p>	<p>30 September 2023, 30 September 2024</p> <hr/> <p>30 September 2025</p>

Table Part III.2: Planned Effectiveness Studies (required additional pharmacovigilance activities)

Study/Status	Summary of objectives	Effectiveness uncertainties addressed	Milestones	Due dates
2019nCoV-401 EU/EEA Post-Authorisation Effectiveness Study Based on a Test-Negative Design Using the COVIDRIVE Platform Ongoing	<ul style="list-style-type: none"> • To estimate CVE of Nuvaxovid against hospitalisation due to laboratory-confirmed SARS-CoV-2 in severe acute respiratory infection (SARI) patients who have completed their primary vaccination series, compared to unvaccinated patients. • To estimate CVE of Nuvaxovid against hospitalisation due to laboratory-confirmed SARS-CoV-2 in SARI patients who previously completed at least a primary series with any COVID-19 vaccine and have received at least one additional dose of Nuvaxovid compared to <ul style="list-style-type: none"> a) unvaccinated patients b) patients who previously completed at least a primary series with any COVID-19 vaccine but did not receive the last additional dose. • To estimate CVE across brands against hospitalisation due to laboratory-confirmed SARS-CoV-2 in SARI patients who previously completed at least a primary series with any COVID-19 vaccine but who did not receive the last additional dose, compared to unvaccinated patients. 	COVID-19 vaccine effectiveness in real-world setting	Interim reports	31 July 2023, 31 January 2024, 31 July 2024
			Final report	31 January 2025

Table Part III.2: Planned Effectiveness Studies (required additional pharmacovigilance activities)

Study/Status	Summary of objectives	Effectiveness uncertainties addressed	Milestones	Due dates
2019nCoV-403 US Post-authorization Effectiveness Study Using a Claims and/or EHR Database Planned	Primary objective: To estimate the effectiveness of the Novavax COVID-19 Vaccine, Adjuvanted in preventing COVID-19 hospitalisations compared to unvaccinated individuals. Secondary objectives: <ul style="list-style-type: none"> • To estimate the effectiveness of the Novavax COVID-19 Vaccine, Adjuvanted in reducing clinically defined laboratory-confirmed severe SARS-CoV-2 infection (i.e., cases that resulted in hospitalisation, admission to the ICU, and/or death) • To assess the effectiveness of the Novavax COVID-19 Vaccine, Adjuvanted: <ul style="list-style-type: none"> ○ after a single dose in reducing clinically defined SARS-CoV-2 infection ○ against SARS-CoV-2 variants (where data is available) ○ by subgroups defined by age, sex, race/ethnicity, comorbidities/coinfections, prior SARS-CoV-2 infection, concomitant vaccinations, concomitant medications, and/or other characteristics 	COVID-19 vaccine effectiveness in real-world setting	Interim reports	30 September 2023, 30 September 2024
			Final report	30 September 2025

Part IV: Plans for post-authorisation efficacy studies

Not applicable.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Important identified risks	
Myocarditis and/or pericarditis	<p><u>Routine risk communication:</u> SmPC section 4.4 and 4.8. PL section 2 and 4.</p> <p><u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> SmPC section 4.4 and PL sections 2 and 4: Recommendation to seek immediate medical attention if symptoms of myocarditis or pericarditis occur.</p> <p><u>Other routine risk minimisation measures beyond the Product Information:</u> None</p>
Important potential risks	
Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)	<p><u>Routine risk communication:</u> None</p> <p><u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> None</p> <p><u>Other routine risk minimisation measures beyond the Product Information:</u> None</p>
Missing information	
Use in pregnancy and while breastfeeding	<p><u>Routine risk communication:</u> SmPC section 4.6 and 5.3 PL section 2</p> <p><u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> None</p> <p><u>Other routine risk minimisation measures beyond the Product Information:</u> None</p>

Table Part V.1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Use in immunocompromised patients	<u>Routine risk communication:</u> SmPC Section 4.4 PL section 2 <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> None <u>Other routine risk minimisation measures beyond the Product Information:</u> None
Use in frail patients with comorbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)	<u>Routine risk communication:</u> None <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> None <u>Other routine risk minimisation measures beyond the Product Information:</u> None
Use in patients with autoimmune or inflammatory disorders	<u>Routine risk communication:</u> PL section 2 <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> None <u>Other routine risk minimisation measures beyond the Product Information:</u> None
Interaction with other vaccines	<u>Routine risk communication:</u> SmPC Sections 4.5 and 5.1 PL section 2 <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> None <u>Other routine risk minimisation measures beyond the Product Information:</u> None
Long-term safety	<u>Routine risk communication:</u> None <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> None <u>Other routine risk minimisation measures beyond the Product Information:</u> None

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in [Part V.1.](#) are sufficient to manage the safety concerns of the medicinal product.

V.3. Summary of Risk Minimisation Measures

Table Part V.2: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important identified risks		
Myocarditis and/or pericarditis	<p><u>Routine risk minimisation measures:</u> SmPC section 4.4 and 4.8. PL section 2 and 4.</p> <p><u>Additional risk minimisation measures:</u> None</p>	<p><u>Routine pharmacovigilance activities beyond ADR reporting and signal detection:</u> <i>Specific adverse reaction follow-up questionnaire</i></p> <p><u>Additional pharmacovigilance activities:</u></p> <p>Ongoing clinical trials 2019nCoV-101 (Part 2); final CSR estimated date 31 December 2023 2019nCoV-501; final CSR estimated date 31 March 2023 2019nCoV-302; final CSR estimated date 31 March 2023 2019nCoV-505; final CSR estimated date 30 November 2023 2019nCoV-311; final CSR estimated date 31 March 2024 2019nCoV-301; final CSR estimated date 31 December 2023</p> <p>Post-authorisation studies 2019nCoV-402 (Safety study using the CPRD Aurum database); final study report estimated date 30 June 2025 2019nCoV-404 (Safety study using a <u>US</u>-based claims and/or EHR database); final study report estimated date 30 September 2025</p>

Table Part V.2: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important potential risks		
<p>Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)</p>	<p><u>Routine risk minimisation measures:</u> None</p> <p><u>Additional risk minimisation measures:</u> None</p>	<p><u>Routine pharmacovigilance activities beyond ADR reporting and signal detection:</u> <i>Specific adverse reaction follow-up questionnaire</i></p> <p><u>Additional pharmacovigilance activities:</u></p> <p>Ongoing clinical trials 2019nCoV-101 (Part 2); final CSR estimated date 31 December 2023 2019nCoV-501; final CSR estimated date 31 March 2023 2019nCoV-302; final CSR estimated date 31 March 2023 2019nCoV-505; final CSR estimated date 30 November 2023 2019nCoV-311; final CSR estimated date 31 March 2024 2019nCoV-301; final CSR estimated date 31 December 2023</p> <p>Post-authorisation studies 2019nCoV-402 (Safety study using the CPRD Aurum database); final study report estimated date 30 June 2025 2019nCoV-404 (Safety study using a <u>US</u>-based claims and/or EHR database); final study report estimated date 30 September 2025</p>
Missing information		
<p>Use in pregnancy and while breastfeeding</p>	<p><u>Routine risk minimisation measures:</u> SmPC Sections 4.6 and 5.3 PL Section 2</p> <p><u>Additional risk minimisation measures:</u> None</p>	<p><u>Routine pharmacovigilance activities beyond ADR reporting and signal detection:</u> None</p> <p><u>Additional pharmacovigilance activities:</u></p> <p>Post-authorisation studies 2019nCoV-405 (Global Pregnancy and infant outcomes study using the “COVID-19 Vaccines <u>International</u> Pregnancy Exposure Registry” (C-VIPER)); final study report estimated date 30 June 2027</p>

Table Part V.2: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Use in immunocompromised patients	<p><u>Routine risk minimisation measures:</u> SmPC Section 4.4 PL section 2</p> <p><u>Additional risk minimisation measures:</u> None</p>	<p><u>Routine pharmacovigilance activities beyond ADR reporting and signal detection:</u> None</p> <p><u>Additional pharmacovigilance activities:</u></p> <p>Ongoing clinical trials 2019nCoV-501; final CSR estimated date 31 March 2023 2019nCoV-302; final CSR estimated date 31 March 2023 2019nCoV-505; final CSR estimated date 30 November 2023 2019nCoV-301; final CSR estimated date 31 December 2023</p> <p>Post-authorisation studies 2019nCoV-402 (Safety study using the CPRD Aurum database); final study report estimated date 30 June 2025 2019nCoV-404 (Safety study using a <u>US</u>-based claims and/or EHR database); final study report estimated date 30 September 2025</p>
Use in frail patients with comorbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)	<p><u>Routine risk minimisation measures:</u> None</p> <p><u>Additional risk minimisation measures:</u> None</p>	<p><u>Routine pharmacovigilance activities beyond ADR reporting and signal detection:</u> None</p> <p><u>Additional pharmacovigilance activities:</u></p> <p>Post-authorisation studies 2019nCoV-402 (Safety study using the CPRD Aurum database); final study report estimated date 30 June 2025 2019nCoV-404 (Safety study using a <u>US</u>-based claims and/or EHR database); final study report estimated date 30 September 2025</p>
Use in patients with autoimmune or inflammatory disorders	<p><u>Routine risk minimisation measures:</u> PL section 2</p> <p><u>Additional risk minimisation measures:</u> None</p>	<p><u>Routine pharmacovigilance activities beyond ADR reporting and signal detection:</u> None</p> <p><u>Additional pharmacovigilance activities:</u></p> <p>Post-authorisation studies 2019nCoV-402 (Safety study using the CPRD Aurum database); final study report estimated date 30 June 2025 2019nCoV-404 (Safety study using a <u>US</u>-based claims and/or EHR database); final study report estimated date 30 September 2025</p>

Table Part V.2: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Interaction with other vaccines	<p><u>Routine risk minimisation measures:</u> SmPC Section 4.5 and 5.1 PL section 2</p> <p><u>Additional risk minimisation measures:</u> None</p>	<p><u>Routine pharmacovigilance activities beyond ADR reporting and signal detection:</u> None</p> <p><u>Additional pharmacovigilance activities:</u></p> <p>Ongoing clinical trials 2019nCoV-302; final CSR estimated date 31 March 2023</p> <p>Post-authorisation studies 2019nCoV-402 (Safety study using the CPRD Aurum database); final study report estimated date 30 June 2025 2019nCoV-404 (Safety study using a <u>US</u>-based claims and/or EHR database); final study report estimated date 30 September 2025</p>
Long-term safety	<p><u>Routine risk minimisation measures:</u> None</p> <p><u>Additional risk minimisation measures:</u> None</p>	<p><u>Routine pharmacovigilance activities beyond ADR reporting and signal detection:</u> None</p> <p><u>Additional pharmacovigilance activities:</u></p> <p>Ongoing clinical trials 2019nCoV-101 (Part 2); final CSR estimated date 31 December 2023 2019nCoV-501; final CSR estimated date 31 March 2023 2019nCoV-302; final CSR estimated date 31 March 2023 2019nCoV-311; final CSR estimated date 31 March 2024 2019nCoV-301; final CSR estimated date 31 December 2023</p> <p>Post-authorisation studies 2019nCoV-402 (Safety study using the CPRD Aurum database); final study report estimated date 30 June 2025 2019nCoV-404 (Safety study using a <u>US</u>-based claims and/or EHR database); final study report estimated date 30 September 2025</p>

Part VI: Summary of the risk management plan

SUMMARY OF RISK MANAGEMENT PLAN FOR NUVAXOVID (COVID-19 VACCINE (RECOMBINANT, ADJUVANTED))

This is a summary of the RMP for Nuvaxovid. The RMP details important risks of Nuvaxovid, how these risks can be minimised, and how more information will be obtained about Nuvaxovid's risks and uncertainties (missing information).

Nuvaxovid's SmPC and its package leaflet give essential information to HCPs and patients on how Nuvaxovid should be used.

This summary of the RMP for Nuvaxovid should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of the Nuvaxovid RMP.

I. The medicine and what it is used for

Nuvaxovid is authorised for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older (see SmPC for the full indication). It contains SARS-CoV-2 spike protein and is adjuvanted with Matrix-M as the active substance and it is given by intramuscular (IM) injection.

Further information about the evaluation of Nuvaxovid's benefits can be found in Nuvaxovid's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <https://www.ema.europa.eu/en/medicines/human/EPAR/nuvaxovid>.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Nuvaxovid, together with measures to minimise such risks and the proposed studies for learning more about Nuvaxovid risks, are outlined below. Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and HCPs;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment and Summary Safety Reports so that immediate action can be taken as necessary. These measures constitute routine PV activities.

If important information that may affect the safe use of Nuvaxovid is not yet available, it is listed under ‘missing information’ below.

II.A List of important risks and missing information

Important risks of Nuvaxovid are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Nuvaxovid. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	Myocarditis and/or pericarditis
Important potential risks	Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)
Missing information	Use in pregnancy and while breastfeeding Use in immunocompromised patients Use in frail patients with comorbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders Interaction with other vaccines Long-term safety

II.B Summary of Important Risks

Important Identified Risk: Myocarditis and/or Pericarditis	
Evidence for linking the risk to the medicine	Literature on COVID-19 vaccines, post-market safety data, and clinical trial data.
Risk factors and risk groups	Adolescent and young adult males following the second dose of vaccine may be at higher risk. Immunocompromised patients may be at a higher risk.
Risk minimisation measures	<p><u>Routine risk minimisation measures:</u> SmPC section 4.4 and 4.8. PL section 2 and 4.</p> <p><u>Additional risk minimisation measures:</u> None</p>
Additional pharmacovigilance activities	<p><u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> <i>Specific adverse reaction follow-up questionnaire</i></p> <p><u>Additional pharmacovigilance activities:</u></p> <p>Ongoing clinical trials 2019nCoV-101 (Part 2); final CSR estimated date 31 December 2023 2019nCoV-501; final CSR estimated date 31 March 2023 2019nCoV-302; final CSR estimated date 31 March 2023 2019nCoV-505; final CSR estimated date 30 November 2023 2019nCoV-311; final CSR estimated date 31 March 2024 2019nCoV-301; final CSR estimated date 31 Dec 2023</p> <p>Post-authorisation studies 2019nCoV-402 (Safety study using the CPRD Aurum database); final study report estimated date 30 June 2025 2019nCoV-404 (Safety study using a <u>US</u>-based claims and/or electronic health records (EHR) database); final study report estimated date 30 September 2025</p>

Important potential risk: Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)	
Evidence for linking the risk to the medicine	<p>Literature on viral vaccines, safety information of other COVID-19 vaccines, clinical trials.</p> <p>Vaccine-associated enhanced disease (VAED) has been rarely encountered with existing vaccines or viral infections. It was observed in children given formalin-inactivated whole-virus vaccines against RSV and measles virus. No events of VAED/VAERD have been reported in the current Nuvaxovid clinical development programme. There is a theoretical concern that vaccination against SARS-CoV-2 may be associated with enhanced severity of COVID-19 episodes which would manifest as VAED/VAERD.</p>
Risk factors and risk groups	<p>There are no known risk factors or specific risk populations identified for VAED/VAERD. The demonstration of some disease enhancement with any candidate vaccine after viral challenge in animal models should not necessarily represent a no-go signal for deciding whether to progress into early trials in clinical development of a COVID-19 vaccine (Lambert 2020). Population-based surveillance might give more insight in this, should any VAED occur.</p>
Risk minimisation measures	<p><u>Routine risk minimisation measures:</u></p> <p>None</p> <p><u>Additional risk minimisation measures:</u></p> <p>None</p>
Additional pharmacovigilance activities	<p><u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u></p> <p><i>Specific adverse reaction follow-up questionnaire</i></p> <p><u>Additional pharmacovigilance activities:</u></p> <p>Ongoing clinical trials</p> <p>2019nCoV-101 (Part 2); final CSR estimated date 31 December 2023</p> <p>2019nCoV-501; final CSR estimated date 31 March 2023</p> <p>2019nCoV-302; final CSR estimated date 31 March 2023</p> <p>2019nCoV-505; final CSR estimated date 30 November 2023</p> <p>2019nCoV-311; final CSR estimated date 31 March 2024</p> <p>2019nCoV-301; final CSR estimated date 31 December 2023</p> <p>Post-authorisation studies</p> <p>2019nCoV-402 (Safety study using the CPRD Aurum database); final study report estimated date 30 June 2025</p> <p>2019nCoV-404 (Safety study using a <u>US</u>-based claims and/or electronic health records (EHR) database); final study report estimated date 30 September 2025</p>

Important missing information: Use in pregnancy and while breastfeeding	
Evidence for linking the risk to the medicine	<p>There is limited experience with use of Nuvaxovid in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition, or post-natal development. Administration of Nuvaxovid in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and foetus.</p> <p><u>Breastfeeding</u></p> <p>It is unknown whether Nuvaxovid is excreted in human milk.</p> <p><u>Fertility</u></p> <p>Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.</p>
Risk factors and risk groups	Pregnant and breastfeeding women
Risk minimisation measures	<p><u>Routine risk communication:</u></p> <p>SmPC Sections 4.6 and 5.3 PL Section 2</p> <p><u>Additional risk minimisation:</u></p> <p>None</p>
Additional pharmacovigilance activities	<p><u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u></p> <p>None</p> <p><u>Additional pharmacovigilance activities:</u></p> <p>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</p>

Important missing information: Use in immunocompromised patients	
Evidence for linking the risk to the medicine	The vaccine has not been studied in individuals with immunocompromised conditions, except for subjects with HIV. Subjects with HIV were not excluded from the clinical programme, and 244 were enrolled in the 2019nCoV-501 study. The safety profile of Nuvaxovid in HIV-positive participants in this study was similar to that seen in HIV-negative participants. There is no evidence that the safety profile of this population receiving Nuvaxovid will be different to that of the general population, but given the paucity of data, the possibility cannot be excluded.
Risk factors and risk groups	Individuals with compromised immune function due to acquired or genetic conditions or conditions requiring the use of immunosuppressants
Risk minimisation measures	<p><u>Routine risk minimisation measures:</u> SmPC Section 4.4 PL section 2</p> <p><u>Additional risk minimisation measures:</u> None</p>
Additional pharmacovigilance activities	<p><u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> None</p> <p><u>Additional pharmacovigilance activities:</u></p> <p>Ongoing clinical trials 2019nCoV-501; final CSR estimated date 31 March 2023 2019nCoV-302; final CSR estimated date 31 March 2023 2019nCoV-505; final CSR estimated date 30 November 2023 2019nCoV-301; final CSR estimated date 31 December 2023</p> <p>Post-authorisation studies 2019nCoV-402 (Safety study using the CPRD Aurum database); final study report estimated date 30 June 2025 2019nCoV-404 (Safety study using a <u>US</u>-based claims and/or electronic health records (EHR) database); final study report estimated date 30 September 2025</p>

Important missing information: Use in frail patients with comorbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)	
Evidence for linking the risk to the medicine	The vaccine has not been studied in frail individuals with comorbidities that may compromise immune function due to the condition or treatment of the condition. Frail patients with comorbidities (e.g., chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders) are potentially at risk of developing a more severe manifestation of COVID-19. There is no evidence that the safety profile of this population receiving Nuvaxovid will be different to that of the general population, but given the paucity of data, the possibility cannot be excluded
Risk factors and risk groups	Frail individuals with comorbidities (e.g., chronic obstructive pulmonary disease (COPD), obesity defined as BMI \geq 30 kg/m ² , DM2, cardiovascular disease, chronic kidney disease or HIV).
Risk minimisation measures	<p><u>Routine risk minimisation measures:</u></p> <p>None</p> <p><u>Additional risk minimisation measures:</u></p> <p>None</p>
Additional pharmacovigilance activities	<p><u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u></p> <p>None</p> <p><u>Additional pharmacovigilance activities:</u></p> <p>Post-authorisation studies</p> <p>2019nCoV-402 (Safety study using the CPRD Aurum database); final study report estimated date 30 June 2025</p> <p>2019nCoV-404 (Safety study using a <u>US</u>-based claims and/or electronic health records (EHR) database); final study report estimated date 30 September 2025</p>

Important missing information: Use in patients with autoimmune or inflammatory disorders	
Evidence for linking the risk to the medicine	There is limited information on the safety of the vaccine in patients with autoimmune or inflammatory disorders. There is no evidence from Nuvaxovid 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.
Risk factors and risk groups	Patients with autoimmune or inflammatory disorders
Risk minimisation measures	<u>Routine risk minimisation measures:</u> PL section 2 <u>Additional risk minimisation measures:</u> None
Additional pharmacovigilance activities	<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> None <u>Additional pharmacovigilance activities:</u> Post-authorisation studies 2019nCoV-402 (Safety study using the CPRD Aurum database); final study report estimated date 30 June 2025 2019nCoV-404 (Safety study using a <u>US</u> -based claims and/or electronic health records (EHR) database); final study report estimated date 30 Sep 2025

Important missing information: Interaction with other vaccines	
Evidence for linking the risk to the medicine	There is limited information on the safety of the vaccine when administered other vaccines within 28 days prior to the first dose or any dose of Nuvaxovid, except for seasonal influenza vaccine, <14 days. Approximately 400 participants were concomitantly administered a seasonal influenza vaccine with Nuvaxovid or placebo. The binding antibody response to SARS-CoV-2 was lower when Nuvaxovid was given concomitantly with inactivated influenza vaccine. The clinical significance of this is unknown.
Risk factors and risk groups	Individuals who will receive other vaccines within 28 prior to 14 days after immunisation with Nuvaxovid.
Risk minimisation measures	<p><u>Routine risk minimisation measures:</u> SmPC Section 4.5 and 5.1 PL section 2</p> <p><u>Additional risk minimisation measures:</u> None</p>
Additional pharmacovigilance activities	<p><u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> None</p> <p><u>Additional pharmacovigilance activities:</u></p> <p>Ongoing clinical trials 2019nCoV-302; final CSR estimated date 31 March 2023</p> <p>Post-authorisation studies 2019nCoV-402 (Safety study using the CPRD Aurum database); final study report estimated date 30 June 2025 2019nCoV-404 (Safety study using a <u>US</u>-based claims and/or electronic health records (EHR) database); final study report estimated date 30 September 2025</p>

Important missing information: Long-term safety	
Evidence for linking the risk to the medicine	Understanding of the long-term safety profile of Nuvaxovid is currently limited. The median duration of safety follow-up in each of the 2 Phase 3 studies was at least 60 days. Follow-up was conducted for one year post-vaccination (Studies 101 Part 1 and 2, 501, and 302) or 2 years post-vaccination (Study 301).
Risk factors and risk groups	There are no known risks with a potentially delayed onset, with the exception of the theoretical concern of VAED/VAERD. Whilst there is currently no evidence to suspect an adverse long-term safety profile, given the paucity of data, the possibility cannot be excluded
Risk minimisation measures	<u>Routine risk minimisation measures:</u> None <u>Additional risk minimisation measures:</u> None
Additional pharmacovigilance activities	<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> None <u>Additional pharmacovigilance activities:</u> Ongoing clinical trials 2019nCoV-101 (Part 2); final CSR estimated date 31 December 2023 2019nCoV-501; final CSR estimated date 31 March 2023 2019nCoV-302; final CSR estimated date 31 March 2023 2019nCoV-311; final CSR estimated date 31 March 2024 2019nCoV-301; final CSR estimated date 31 December 2023 Post-authorisation studies 2019nCoV-402 (Safety study using the CPRD Aurum database); final study report estimated date 30 June 2025 2019nCoV-404 (Safety study using a US-based claims and/or electronic health records (EHR) database); final study report estimated date 30 September 2025

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies that are conditions of the marketing authorisation or specific obligation of Nuvaxovid.

II.C.2 Other studies in post-authorisation development plan

Study: 2019nCoV-101 (Part 2)

Purpose of the study:

To evaluate the safety and immunogenicity of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine (SARS-CoV-2 rS) with or without Matrix-M adjuvant in healthy subjects.

Study: 2019nCoV-501

Purpose of the study:

To evaluate the efficacy, immunogenicity, and safety of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine (SARS-CoV-2 rS) with Matrix-M adjuvant in South African adult subjects living without HIV; and safety and immunogenicity in adults living with HIV.

Study: 2019nCoV-302

Purpose of the study:

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

Study: 2019nCoV-505

Purpose of the study:

To evaluate the safety and immunogenicity of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine (SARS-CoV-2 rS) with Matrix-M adjuvant in people living with HIV and without HIV.

Study: 2019nCoV-311

Purpose of the study:

To evaluate the safety and immunogenicity of 2 booster doses of the monovalent prototype vaccine (NVX-CoV2373), monovalent Omicron subvariant vaccines (NVX-CoV2515 [BA.1] and NVX-CoV2540 [BA.5]) and bivalent vaccines (NVX-CoV2373 + NVX-CoV2515 and NVX-CoV2373 + NVX-CoV2540) participants who have already been immunized with 2 or 3 doses of the Moderna or Pfizer/BioNTech prototype vaccines. Additionally, the study will investigate the ability of the NVX-CoV2515 vaccine to demonstrate a statistically superior difference in the titers of cross-neutralizing antibodies and IgG antibodies compared to the NVX-CoV2373 prototype vaccine.

Study: 2019nCoV-301

Purpose of the study:

To evaluate the efficacy of a two-dose regimen of SARS-CoV-2 rS adjuvanted with Matrix-M compared to placebo against 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. Evaluate the efficacy and safety after vaccination with SARS-CoV-2 rS adjuvanted with Matrix-M compared to placebo in paediatric participants 12 to <18 years of age. Evaluate the safety and immunogenicity following a single booster dose approximately 6 months following active vaccination in adults and adolescents. Evaluate the safety and immunogenicity following a second booster dose approximately 6 months following the first booster vaccination in a sub-study of adults enrolled in the study.

Study: 2019nCoV-402 (Post-Authorisation Safety Study Using the Clinical Practice Research Datalink (CPRD))

Purpose of the study:

To evaluate the risk of select safety outcomes of interest following vaccination with the Nuvaxovid using a (i) a self-controlled case series (SCCS) design and (ii) a comparative cohort study design.

Study: 2019nCoV-405 (Global Pregnancy and Infant Outcomes Study Using the COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER))

Purpose of the study:

To estimate the risk of obstetric outcomes and infant outcomes among pregnant women exposed to a single (homologous) or mixed (heterologous) Nuvaxovid series from 30 days prior to the first day of the last menstrual period (LMP) to end of pregnancy and their offspring relative to a matched reference group who received no COVID-19 vaccinees during pregnancy.

Study: 2019nCoV-404 (US Post-authorisation safety study using a claims and/or EHR database)

Purpose of the study:

To evaluate the risk of select AESIs following vaccination with at least one dose of the Novavax COVID-19 Vaccine, Adjuvanted using SCCS and cohort study designs.

Study: 2019-nCoV-401 (EU Post-Authorisation Effectiveness Study Based on a Test-Negative Design Using the COVIDRIVE Platform)

Purpose of the study:

To estimate COVID-19 vaccine effectiveness (CVE) of Nuvaxovid against hospitalisation due to laboratory-confirmed SARS-CoV-2 in severe acute respiratory infection (SARI) patients who have completed their primary vaccination series, compared to unvaccinated patients. Additionally, the study will estimate CVE of Nuvaxovid against hospitalisation due to laboratory-confirmed SARS-CoV-2 in SARI patients who previously completed at least a primary series with any COVID-19 vaccine compared to a) unvaccinated patients and b) patients who previously completed at least a primary series with any COVID-19 vaccine but did not receive the last additional dose. Further, the study will estimate CVE across brands against hospitalisation due to laboratory-confirmed SARS-CoV-2 in SARI patients who previously completed at least a primary series with any COVID-19 vaccine but who did not receive the last additional dose, compared to unvaccinated patients.

Study: 2019nCoV-403 (US Post-authorisation Effectiveness Study Using a Claims and/or EHR Database)

Purpose of the study:

To estimate the effectiveness of the Novavax COVID-19 Vaccine, Adjuvanted in preventing COVID-19 hospitalisations compared to unvaccinated individuals.

Annex 4: Specific adverse drug reaction follow-up questionnaire examples

[Annex 4.A: Vaccine-associated enhanced disease \(VAED\), including vaccine-associated enhanced respiratory disease \(VAERD\) questionnaire](#)

[Annex 4.B: Myocarditis/pericarditis questionnaire](#)

VACCINE ASSOCIATED ENHANCED DISEASE QUESTIONNAIRE

1. Reporter Information:

Reporter's First and Last Name:

Is the Reporter a Healthcare Professional Yes No

If yes, what is the specialty:

Reporter's Address (no, street, city, postal code, country):

Reporter's Telephone and Fax:

Reporter's Signature and Date (DD/MM/YYYY):

2. Patient Details:

Initials:

Sex: Male Female

Date of Birth (DD/MM/YYYY):

Age in Years:

Race: White Black or African American Native American Alaska Native Native Hawaiian
 Asian Other _____ Refused or Unknown

Ethnicity: Hispanic or Latino Not Hispanic or Latino Other _____ Unknown

3. Covid-19 Vaccine Novavax:

Dose 1 received Yes No If yes, date of vaccination (DD/MM/YY):

Batch/Lot number:

Dose 2 received Yes No If yes, date of vaccination (DD/MM/YY):

Batch/Lot number:

If dose 2 was not received, was the dose not administered due to the adverse event? Yes | No

4. Adverse Event Details:

Adverse Event(s)	Start Date (DD/MM/YY)	Stop Date (DD/MM/YY)	Outcome
			<input type="checkbox"/> Recovered <input type="checkbox"/> Event ongoing <input type="checkbox"/> Recovering <input type="checkbox"/> Resolved with sequelae, <i>please specify</i> <input type="checkbox"/> Patient died <input type="checkbox"/> Unknown
			<input type="checkbox"/> Recovered <input type="checkbox"/> Event ongoing <input type="checkbox"/> Recovering <input type="checkbox"/> Resolved with sequelae, <i>please specify</i> <input type="checkbox"/> Patient died <input type="checkbox"/> Unknown

Please provide details of any signs and symptoms experienced in relation to diagnosed or suspected COVID-19 illness (including date of onset for each and eventual worsening):

SARS-CoV-2 test/antibodies:

Did the patient have testing for SARS-CoV-2? Yes No Unknown
If yes, specify type of testing and date of test, whether IgM /IgG or both and the titer:

PCR test result:

Variant type if known:

Viral load (including Cycle Threshold):

In the absence of a positive test, what findings suggested a diagnosis of COVID-19 infection or VAED?

Does the patient have SARS-CoV-2 antibodies at diagnosis? Yes No Unknown

How many days from the SARS-CoV2 diagnosis did it take before the SARS-CoV2 antigen test became negative

In the event of death, please provide the date and cause of death (*please provide copy of autopsy report, if available*):

Was the patient hospitalized for the adverse event(s)? Yes No
 If yes, please provide the admission and the discharge dates (*DD/MM/YY*)

Please provide the discharge report information and histology results
 Was/Is the patient admitted to an Intensive Care Unit? Yes No Unknown
If 'Yes', please provide case summary:

Have any pre-existing diseases worsened during the SARS-CoV-2 Yes No Unknown
If 'Yes', please specify the details:

5. Patient Covid-19 Treatment:

Therapy	Start Date (DD/MM/YY)	Stop Date (DD/MM/YY)	Daily dose/ Any additional information
Remdesivir			
Hydroxychloroquine			
Monoclonal antibodies			
Azithromycin			
Corticosteroids			
Bamlavinimab			
Etesevimab			
Plasmapheresis			
Other (please specify)			

6. Please provide information on any new or worsening symptoms/signs during the COVID-19 illness:

Respiratory	Cardio-Vascular	Hematology & Immune system	Renal system	Gastro-intestinal and hepatic system	Central nervous system	Other systems
<input type="checkbox"/> Dyspnea <input type="checkbox"/> Tachypnea <input type="checkbox"/> Hypoxemia <input type="checkbox"/> Cough <input type="checkbox"/> Cyanosis <input type="checkbox"/> COVID-19 pneumonia <input type="checkbox"/> Acute respiratory distress syndrome <input type="checkbox"/> Lower respiratory tract infection <input type="checkbox"/> Respiratory failure <input type="checkbox"/> Pulmonary hemorrhage <input type="checkbox"/> Radiographic abnormalities <input type="checkbox"/> Other:	<input type="checkbox"/> Heart failure <input type="checkbox"/> Acute cardiac injury <input type="checkbox"/> Acute myocardial infarction <input type="checkbox"/> Arrhythmia <input type="checkbox"/> Pericarditis <input type="checkbox"/> Myocarditis <input type="checkbox"/> Cardiogenic shock <input type="checkbox"/> Other:	<input type="checkbox"/> Coagulopathy <input type="checkbox"/> Thrombocytopenia <input type="checkbox"/> Deep vein thrombosis <input type="checkbox"/> Disseminated intravascular coagulation <input type="checkbox"/> Vasculitis <input type="checkbox"/> Limb ischemia <input type="checkbox"/> Pulmonary embolism <input type="checkbox"/> Other:	<input type="checkbox"/> Renal disfunction <input type="checkbox"/> Acute kidney injury <input type="checkbox"/> Other:	<input type="checkbox"/> Vomiting <input type="checkbox"/> Diarrhea <input type="checkbox"/> Jaundice <input type="checkbox"/> Abdominal pain <input type="checkbox"/> Acute liver injury <input checked="" type="checkbox"/> Other:	<input type="checkbox"/> Altered mental status <input type="checkbox"/> Convulsions/seizures <input type="checkbox"/> Cranial nerve involvement <input type="checkbox"/> Encephalopathy <input type="checkbox"/> Meningitis <input type="checkbox"/> Cerebrovascular accident <input type="checkbox"/> Other:	<input type="checkbox"/> Acute arthritis <input type="checkbox"/> Dermatologic <input type="checkbox"/> Chilblains <input type="checkbox"/> Erythema multiforme <input type="checkbox"/> Multisystem inflammatory syndrome <input type="checkbox"/> Multiorgan failure <i>Specify:</i> <input type="checkbox"/> Death <input type="checkbox"/> Other:

7. Relevant Medical History / Concurrent Diseases:

Medical History	Start Date	Stop Date	Is the patient treated for this condition?
Respiratory or gastrointestinal infection <input type="checkbox"/> Yes <input type="checkbox"/> No			
Lymphoma <input type="checkbox"/> Yes <input type="checkbox"/> No			
HIV positive <input type="checkbox"/> Yes <input type="checkbox"/> No			
Systemic lupus erythematosus <input type="checkbox"/> Yes <input type="checkbox"/> No			
Vasculitis <input type="checkbox"/> Yes <input type="checkbox"/> No			
Other autoimmune disorders <input type="checkbox"/> Yes <input type="checkbox"/> No			
Hypertension <input type="checkbox"/> Yes <input type="checkbox"/> No			
Diabetes <input type="checkbox"/> Yes <input type="checkbox"/> No			
Heart Disease (<i>please specify</i>) <input type="checkbox"/> Yes <input type="checkbox"/> No			
Lung Disease (<i>please specify</i>) <input type="checkbox"/> Yes <input type="checkbox"/> No			
Kidney disease (<i>please specify</i>) <input type="checkbox"/> Yes <input type="checkbox"/> No			
Liver disease (<i>please specify</i>) <input type="checkbox"/> Yes <input type="checkbox"/> No			
Coagulation disorders <input type="checkbox"/> Yes <input type="checkbox"/> No			
Obesity <input type="checkbox"/> Yes <input type="checkbox"/> No			
Current or Former Smoker: <i>If yes, please provide details</i> <input type="checkbox"/> Yes <input type="checkbox"/> No			

8. Concomitant Drugs / Vaccines:

Please exclude drugs used to treat the event(s). List all medications taken by the patient, including over-the-counter drugs, supplements, and herbal preparations. Add vaccine administered within the last month

Concomitant Drug Name	Indication	Daily Dose	Route	Start Date (DD/MM/YY)	Stop Date (DD/MM/YY)	Withdrawn
						<input type="checkbox"/> Yes <input type="checkbox"/> No
						<input type="checkbox"/> Yes <input type="checkbox"/> No
						<input type="checkbox"/> Yes <input type="checkbox"/> No
						<input type="checkbox"/> Yes <input type="checkbox"/> No

9. Lab Test / Diagnostic Procedures:

Please provide and attach results of relevant laboratory test and procedures

Lab test /Diagn. Procedure	Date and Results
Imaging for COVID-Pneumonia (e.g., CXR, CT)	
Hypoxemia,OR,Hypercapnia (PaCO ₂) OR acidosis (pH)	
Hematology results	
Chemistry results	
Elevated cytokines	

Thank you for completing this form.

MYOCARDITIS - PERICARDITIS QUESTIONNAIRE

1. Reporter Information:

Reporter's First and Last Name:

Is the Reporter a Healthcare Professional: Yes No

If yes, what is the specialty:

Reporter's Address (no, street, city, postal code, country):

Reporter's Telephone and Fax:

Reporter's Signature and Date (DD/MM/YYYY):

2. Patient Details:

Initials:

Sex: Male Female

Date of Birth (DD/MM/YYYY):

Age in Years:

Race: White Black or African American Native American Alaska Native Native Hawaiian
 Asian Other _____ Refused or Unknown

Ethnicity: Hispanic or Latino Not Hispanic or Latino Other _____ Unknown

3. Covid-19 Vaccine Novavax:

Dose 1 received Yes No If yes, date of vaccination (DD/MM/YY):

Batch/Lot number:

Dose 2 received Yes No If yes, date of vaccination (DD/MM/YY):

Batch/Lot number:

Dose 3 received Yes No If yes, date of vaccination (DD/MM/YY):

Batch/Lot number:

If dose 2 or 3 was not received, was the dose not administered due to the adverse event? Yes | No

4. Adverse Event Details:

Adverse Event(s) (Check any/both as applicable)	Start Date (DD/MM/YY)	Stop Date (DD/MM/YY)	Outcome
<input type="checkbox"/> Myocarditis			<input type="checkbox"/> Recovered <input type="checkbox"/> Event ongoing <input type="checkbox"/> Recovering <input type="checkbox"/> Resolved with sequelae, <i>please specify</i> <input type="checkbox"/> Patient died <input type="checkbox"/> Unknown
<input type="checkbox"/> Pericarditis			<input type="checkbox"/> Recovered <input type="checkbox"/> Event ongoing <input type="checkbox"/> Recovering <input type="checkbox"/> Resolved with sequelae, <i>please specify</i> <input type="checkbox"/> Patient died <input type="checkbox"/> Unknown

Were clinical cardiac symptoms present? (If yes, please circle what is relevant)

Acute chest pain or pressure - Palpitations - Dyspnea after exercise - Dyspnea at rest or lying down – Diaphoresis (excessive sweating)

Were Non-Specific Symptoms present? (If yes, please circle what is relevant)

Fatigue - Abdominal pain - Dizziness/Syncope - Edema - Cough - Weakness - Nausea/Vomiting - Diarrhea - Shoulder/Upper back pain - Cyanosis - Low grade intermittent fever - Altered Mental Status

In Infants and Young Children: Irritability - Vomiting - Poor feeding - Tachypnea – Lethargy

Other: *please specify* _____

In the event of death, *please provide the date and cause of death:* _____

Was an autopsy performed? Yes (*if yes please attach the autopsy report*) No

Was the patient hospitalized for the adverse event(s)? Yes (*if yes, provide date of hospitalization*) _____ No

Is a discharge report available? Yes (*if yes, please attach the report*) No

5. Patient Treatment:

Drug name	Start Date (DD/MM/YY)	Stop Date (DD/MM/YY)	Route	Daily dose/ Any additional information

6. Medical History/Concurrent Diseases (including recent infections):

Medical History (please specify all relevant medical conditions)	Start date	Stop date	Was the patient treated for this condition?

7. Concomitant Drugs/Vaccines:

Please exclude drugs used to treat the event(s). List all medications taken by the patient, including over-the-counter drugs, supplements, and herbal preparations. Add other covid19 vaccine administered previously.

Concomitant Drug Name	Indication	Daily Dose	Route	Start Date (DD/MM/YY)	Stop Date (DD/MM/YY)	Withdrawn
						<input type="checkbox"/> Yes <input type="checkbox"/> No
						<input type="checkbox"/> Yes <input type="checkbox"/> No
						<input type="checkbox"/> Yes <input type="checkbox"/> No
						<input type="checkbox"/> Yes <input type="checkbox"/> No

8. Laboratory Test / Diagnostic Procedure:

Please provide and attach results of relevant laboratory test and procedures

Laboratory test/Diagnostic procedure	Date / Result	Normal Reference Range
Troponin T <input type="checkbox"/> Yes <input type="checkbox"/> No		
Troponin I <input type="checkbox"/> Yes <input type="checkbox"/> No		
Creatine Kinase Myocardial <input type="checkbox"/> Yes <input type="checkbox"/> No		
C-reactive protein <input type="checkbox"/> Yes <input type="checkbox"/> No		
Erythrocyte sedimentation rate <input type="checkbox"/> Yes <input type="checkbox"/> No		
D-Dimer <input type="checkbox"/> Yes <input type="checkbox"/> No		
Cardiac Magnetic Resonance Imaging Study <input type="checkbox"/> Yes <input type="checkbox"/> No		
Echocardiogram <input type="checkbox"/> Yes <input type="checkbox"/> No		
EKG <input type="checkbox"/> Yes <input type="checkbox"/> No		
Radiography <input type="checkbox"/> Yes <input type="checkbox"/> No		
Myocardial Tissue Histopathology/ Endomyocardial biopsy <input type="checkbox"/> Yes <input type="checkbox"/> No		
CT scan <input type="checkbox"/> Yes <input type="checkbox"/> No		
Diagnostic tests for infectious etiologies, including but not limited to COVID-19 <input type="checkbox"/> Yes <input type="checkbox"/> No		
Other, <i>pls specify:</i>		

Thank you for completing this form

Annex 6: Details of proposed additional risk minimisation activities (if applicable)

Not applicable