EU RISK MANAGEMENT PLAN

NUVAXOVID, NUVAXOVID XBB.1.5, AND NUVAXOVID JN.1 (COVID-19 VACCINE (RECOMBINANT, ADJUVANTED))

RMP version number: 5.1

Data lock point (DLP) for this RMP: See below

Date of final sign off: 14 June 2024

Clinical trial data DLP: 04 August 2023*

Post-marketing data DLP: 19 December 2023

Epidemiology data DLP: 31 March 2024

*Per agreement with EMA, data from recently completed clinical trials shall be grouped and included in a future EU RMP update.

Rationale for submitting an updated RMP:

The RMP supports the inclusion of the Nuvaxovid Omicron JN.1 variant strain.

Summary of significant changes in this RMP:

RMP Part/Module	**RMP v5.1**
PART I PRODUCT(S) OVERVIEW	Updated the following sections with variant strain information: Active substance(s), Brief description of the product, Indication in the EEA, Dosage in the EEA, and Pharmaceutical form and strength.
PART II SAFETY SPECIFICATION	
PART II Module SI Epidemiology of the Indication(s) and Target Populations	Updated epidemiology information to include Omicron JN.1 variant strain.
PART II Module SII Non-Clinical Part of the Safety Specification	Updated non-clinical data to support Nuvaxovid JN.1 variant.
PART II Module SIII Clinical Trial Exposure	Update to the status of completed clinical studies.
PART II Module SIV Populations Not Studied in Clinical Trials	No changes.
PART II Module SV Post-Authorisation Experience	Updated 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	Updated to include clinical and post-marketing safety data for safety concerns, as applicable.
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	Updated study milestones for additional PV activities, as applicable.
PART IV PLANS FOR POST AUTHORISATION EFFICACY STUDIES	No changes.

RMP Part/Module	**RMP v5.1**
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	Updated study/milestones as per Part III changes. Updated to reflect Nuvaxovid JN.1variant.
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	Updated 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 Record 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: 4.3

Approved with procedure: EMEA/H/C/005808/II/0060

Date of approval (opinion date): 11 April 2024

EU QPPV name[1]: Julia Appelskog

EU QPPV signature: The content of this RMP has been reviewed and approved by Novavax's QPPV or Deputy QPPV (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
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
DLP	Data Lock Point
DM	Diabetes Mellitus
DME	Designated Medical Event
ECDC	European Centre for Disease Prevention and Control
EHR	Electronic Health Record
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medicines Agency
EoS	End of Study
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
GVP	Good Pharmacovigilance Practices
HCP	HealthCare Professional/Provider
HIV	Human Immunodeficiency Virus
HLT	High Level Term
ICSR	Individual Case Safety Report
ICU	Intensive Care Unit
IR	Incidence Ratio
IM	Intramuscular
IME	Important Medical Event

Acronym	Abbreviation Definition
LTCF	Long term care facility
MedDRA	Medical Dictionary tor Regulatory Activities
MAAE	Medically Attended Adverse Event
MHC	Major Histocompatibility Complex
µg	Microgram(s)
mL	Milliliter(s)
NHP	Non-human primate(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
PLWH	Persons living with HIV
PRAC	Pharmacovigilance Risk Assessment Committee
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
PvSS	Pharmacovigilance Signaling System
QPPV	Qualified Person for Pharmacovigilance
rS	Recombinant Spike
RIVM	Dutch 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
SRR	Seroresponse rate
SY	Subject Year(s)
TND	Test-Negative Design
TEAE	Treatment-Emergent Adverse Event
TTO	Time To Onset

Acronym	Abbreviation Definition
VAED	Vaccine-Associated Enhanced Disease
VAERD	Vaccine-Associated Enhanced Respiratory Disease
VAERS	Vaccine Adverse Event Reporting System

Part I: Product(s) Overview

Table Part I.1 Product(s) Overview

Active substance(s) (INN or common name)	COVID-19 Vaccine (recombinant, adjuvanted) (SARS-CoV-2 Original, Wuhan strain) COVID-19 Vaccine (recombinant, adjuvanted) (SARS-CoV-2 Omicron XBB.1.5) COVID-19 Vaccine (recombinant, adjuvanted) (SARS-CoV-2 Omicron JN.1)
Pharmacotherapeutic group(s) (ATC Code)	COVID-19 vaccine, protein subunit (J07BN04)
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 Nuvaxovid XBB.1.5 dispersion for injection Nuvaxovid JN.1 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.

Table Part I.1 Product(s) Overview

	Important information about its composition: Nuvaxovid: One dose (0.5 milliliters (mL)) contains 5 micrograms (µg) of the SARS-CoV-2 spike protein produced by recombinant DNA technology using a baculovirus expression system in an insect cell line that is derived from Sf9 cells of the *Spodoptera frugiperda* species 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 *Quillaja saponaria* Molina extract. Nuvaxovid XBB.1.5: One dose (0.5 mL) contains 5 µg of the SARS-CoV-2 (Omicron XBB.1.5) spike protein produced by recombinant DNA technology using a baculovirus expression system in an insect cell line that is derived from Sf9 cells of the *Spodoptera frugiperda* species 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 *Quillaja saponaria* Molina extract. Nuvaxovid JN.1: One dose (0.5 mL) contains 5 µg of the SARS-CoV-2 (Omicron JN.1) spike protein produced by recombinant DNA technology using a baculovirus expression system in an insect cell line that is derived from Sf9 cells of the *Spodoptera frugiperda* species 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 *Quillaja saponaria* Molina extract.
Hyperlink to the Product Information	Nuvaxovid/Nuvaxovid XBB.1.5/Nuvaxovid JN.1 dispersion for injection Summary of Product Characteristics (SmPC)
Indication(s) in the EEA	Current for Nuvaxovid: Nuvaxovid is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older. The use of this vaccine should be in accordance with official recommendations. Current for Nuvaxovid XBB.1.5: Nuvaxovid XBB.1.5 is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older. The use of this vaccine should be in accordance with official recommendations.
	Proposed: Nuvaxovid JN.1: Nuvaxovid JN.1 is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older. The use of this vaccine should be in accordance with official recommendations.
Dosage in the EEA	Current for Nuvaxovid: 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.

Table Part I.1 Product(s) Overview

	Booster dose *Booster dose in individuals 12 years of age and older* A booster dose of Nuvaxovid (0.5 mL) may be administered intramuscularly approximately 3 months after the primary series of Nuvaxovid in individuals 12 years of age and older (homologous booster dose). Nuvaxovid may also be given as a booster dose in individuals 18 years of age and older following a primary series comprised of an 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. *Paediatric population* The safety and efficacy of Nuvaxovid in children aged less than 12 years have not yet been established. No data are available. *Elderly population* No dose adjustment is required in elderly individuals ≥ 65 years of age. Current for Nuvaxovid XBB.1.5: Nuvaxovid XBB.1.5 is administered intramuscularly as a single dose (0.5 mL) for individuals 12 years of age and older regardless of previous vaccination status. For individuals who have previously been vaccinated with a COVID-19 vaccine, Nuvaxovid XBB.1.5 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine. *Immunocompromised individuals* Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations. *Paediatric population* The safety and efficacy of Nuvaxovid XBB.1.5 in children aged less than 12 years have not yet been established. No data are available. *Elderly population* No dose adjustment is required in elderly individuals ≥ 65 years of age.
	Proposed: Nuvaxovid JN.1: Nuvaxovid JN.1 is administered intramuscularly as a single dose (0.5 mL) for individuals 12 years of age and older regardless of previous vaccination status. For individuals who have previously been vaccinated with a COVID-19 vaccine, Nuvaxovid JN.1 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine. *Immunocompromised individuals* Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations. *Paediatric population* The safety and efficacy of Nuvaxovid JN.1 in children aged less than 12 years have not yet been established. No data are available. *Elderly population* No dose adjustment is required in elderly individuals ≥ 65 years of age.

Table Part I.1 Product(s) Overview

Pharmaceutical form(s) and strengths	Current for Nuvaxovid: Dispersion for injection in multidose vial of 5 doses or 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). Current for Nuvaxovid XBB.1.5: Single or multidose vials. Dispersion for injection in a single dose vial where each vial contains 1 dose of 0.5 mL. Dispersion for injection in multidose vial where each vial contains 5 doses of 0.5 mL. Each dose contains 5 µg SARS-CoV-2 (Omicron XBB.1.5) spike protein and is adjuvanted with Matrix-M. The dispersion is colourless to slightly yellow, clear to mildly opalescent (pH 7.2).
	Proposed: Nuvaxovid JN.1: Single or multidose vials. Dispersion for injection in a single dose vial where each vial contains 1 dose of 0.5 mL. Dispersion for injection in multidose vial where each vial contains 5 doses of 0.5 mL. Each dose contains 5 µg SARS-CoV-2 (Omicron JN.1) spike protein and is adjuvanted with Matrix-M. The dispersion is colourless to slightly yellow, clear to mildly opalescent (pH 7.2).
Is/will the product be subject to additional monitoring in the EU?	Yes

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:

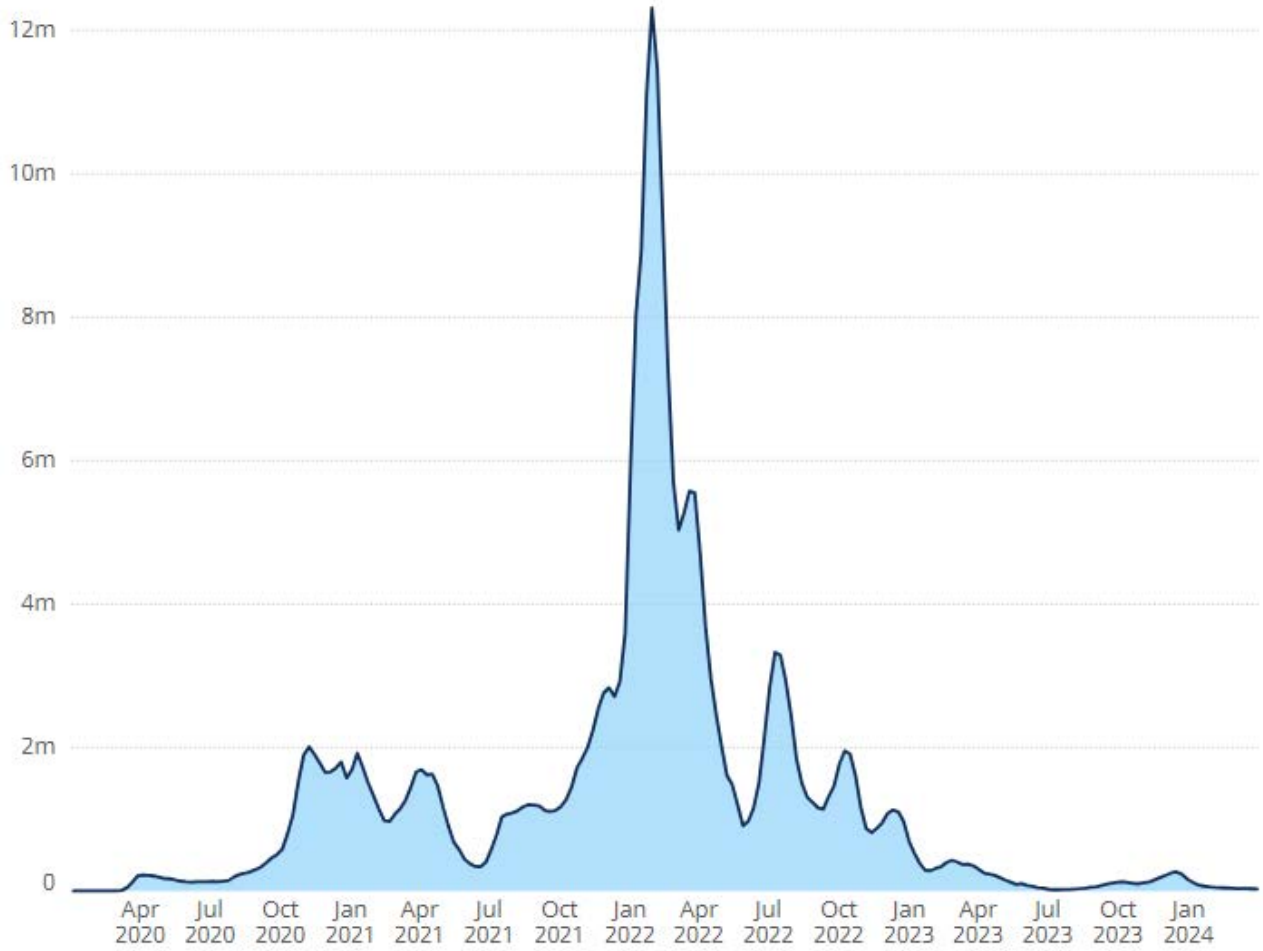
- Individuals 12 years of age and older (Nuvaxovid)
- Individuals 12 years of age and older (Nuvaxovid XBB.1.5)
- Individuals 12 years of age and older (Nuvaxovid JN.1)

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 31 March 2024, there were nearly 775 million confirmed cases of COVID-19 worldwide and over 7.0 million deaths (WHO 2024). In the WHO Region of Europe over the same period, there were more than 279 million cases (Figure SI.1), and nearly 2.3 million deaths.

Figure SI.1: COVID-19 Cases Reported Weekly in WHO Europe (01 January 2020 to 31 March 2024 (WHO 2024)



The reported case counts underestimate the overall burden of SARS-CoV-2, as only a fraction of acute infections 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 hospitalisation 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 360 times as likely to die compared to the 18 – 29 years old reference group (CDC 2023). The risks for hospitalization and death are less than that of the 18 – 29-year-old 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 intensive care unit (ICU), intubation, or mechanical ventilation. Underlying medical conditions that may increase the risk for COVID-19 severity include: asthma, cancer, cerebrovascular disease, chronic kidney disease (CKD), chronic lung diseases (i.e., bronchiectasis, chronic obstructive pulmonary disease [~~(~~COPD]~~)~~, interstitial lung disease, pulmonary embolism, and pulmonary hypertension), chronic liver diseases (i.e., cirrhosis, non-alcoholic fatty liver disease, alcoholic liver disease, and autoimmune hepatitis), heart conditions such as heart failure, coronary artery disease, or cardiomyopathies, cystic fibrosis, immunocompromising conditions (e.g., Human Immunodeficiency Virus [HIV], primary immunodeficiencies, solid organ or blood stem cell transplantation, and medication-induced immunodeficiency), tuberculosis, sickle cell disease, diabetes mellitus, pregnancy, smoking, obesity, and physical inactivity (CDC 2024, RIVM 2023, ECDC 2023a, UK Government 2023).

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 National Institute for Public Health and the Environment (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

The management of COVID-19 is based on the 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 2024a).

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), , Spikevax (Moderna), Nuvaxovid (Novavax), Jcovden (Janssen), and Bimervax (HIPRA Human Health) (EMA 2024b).

In addition, two monoclonal antibodies (i.e., Evusheld and Ronapreve) are authorised for prevention of COVID-19 (EMA 2024a). General preventative measures include social distancing, face masks, and proper hygiene.

Primary Series

As of 05 October 2023, 75.6% of the EU/EEA population had received at least one dose of a COVID-19 vaccine and 73.0% had completed the primary series (country range: 30.1 – 87.1%) (ECDC 2023b). Completion of the primary series was 82.5% among those 18 years and older (country range: 35.8 – 96.5%) and 91.2% among those 60 years and older (country range 38.5 – 100%).

Boosters

As of 05 October 2023, 54.8% of the EU/EEA population had received at least one booster dose, 14.7% had received a second booster dose, and 2.4% had received a third booster dose (ECDC 2023b). Among those 18 years and older, 65.5%,17.9%, and 2.9% had received a first, second, and third booster dose, respectively. Among those 60 years and older, 84.9%, 35.6%, and 4.0% had received a first, second, and third booster dose, respectively.

Clinical Manifestations and Natural History

The most common symptoms include fever, cough, tiredness, and loss of taste or smell (WHO 2023). Less common symptoms include sore throat, headache, aches and pains, diarrhoea, skin rash, and red irritated eyes.

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).

There is evidence that the presentation of COVID-19 symptoms has evolved over time. The prevalence of symptoms that characterize an omicron infection differs from those of the delta variant with less involvement of the lower respiratory tract and reduced probability of hospital admission (Menni 2022). Loss of smell, runny nose, brain fog, eye soreness, headache, fever, hair loss, blistering on feet, ear ringing, and dizziness were less common and sore throat was more common among those infected by omicron subvariants BA.1 and BA.2 compared to those infected during delta prevalence. The change in COVID-19 symptoms and severity may be due to vaccination, immunity from prior infection or the evolution of the virus to cause overall less intense acute infection (Looi 2023). Variant JN.1, a subvariant of Omicron variant BA.2.86, features similar symptoms to other Omicron variants and may be more transmissible but does not appear to result in more severe disease in comparison to other variants (Hemo 2024).

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 four European countries reporting SARS-CoV-2 sequencing or genotyping, the distribution (median proportion and range) of variants of concern or of interest, from 1 April 2024 to 7 April 2024, was estimated to be 93% (54 – 100%%) for BA.2.86 (including JN.1 isolates) and 0% (0-18%) for XBB.1.5-like variants. Of all SARS-CoV-2 isolates that were sequenced during the reporting month, 88% were identified as JN.1 (ERVISS 2024).

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.

To accompany the non-clinical program for the adjuvanted Prototype rS vaccine based on the ancestral strain of SARS-CoV-2 (Wuhan-Hu-1), several immunogenicity studies using adjuvanted Omicron BA.5 rS, XBB.1.5 rS, and other variant vaccines were conducted in mice and non-human primates (NHPs). In immunogenicity studies in mice (702-171 and 702-172), Matrix-M adjuvanted SARS-CoV-2 rS regimens (SARS-CoV-2 Prototype rS, Omicron BA.1 rS, Omicron BA.5 rS, or Omicron BA.2.12.1 rS vaccines administered as a monovalent or bivalent, homologous or heterologous two-dose primary series) induced robust and comparable antibody and T-cell responses in mice. In a baboon immunogenicity study (702-134), interim results indicate that a primary series of monovalent Prototype rS or Omicron BA.1 rS, followed by a booster dose of monovalent Omicron BA.5 rS or Bivalent rS (Prototype rS+ BA.5 rS) with Matrix-M adjuvant induced homologous and cross-reactive antibody and cell-mediated immune responses in baboons, with no notable safety findings. In baboons immunized with the monovalent Prototype rS primary series, a booster dose of monovalent BA.5 rS tended to produce stronger immune responses than boosting with Bivalent rS vaccine. In baboons immunized with a monovalent Omicron BA.1 rS primary series, boosting with monovalent BA.5 rS or bivalent vaccine resulted in similar immunogenicity. Interim results from another study in rhesus macaques (702-173) showed that SARS-CoV-2 Prototype rS and Omicron BA.5 rS administered as a monovalent or bivalent two-dose primary immunization series induced robust functional antibody responses. An 8-month booster dose of monovalent XBB.1.5 rS induced a rapid anamnestic response in these NHPs, resulting in robust functional antibody responses against Omicron XBB.1.5, XBB.1.16, and XBB.2.3. Additionally, Omicron XBB.1.5rS administered as a two-dose primary series and a six-month booster dose with XBB.1.5 rS, followed by a second (11-month) booster dose with Omicron JN.1 rS in rhesus macaques induced robust immunogenicity and functional neutralizing antibody responses against forward-drifted SARS-CoV-2 variants including KQ.1, KP.2, KP.1.1, KP.3, and LA.2. The JN.1 rS booster dose elicited cross-reactive multifunctional CD4+ T cell responses against

forward-drifted variants as well. These data support a COVID-19 vaccine strain change to JN.1 rS for the 2024-2025 season to generate virus neutralizing antibody responses against circulating SARS-CoV-2 variants including those with FLiRT and FLuQUE mutations. Additional immunogenicity studies in mice (702-186, 702-188, and 702-191) evaluating the immunogenicity of monovalent or bivalent Omicron XBB.1.5 rS as a primary series or booster dose demonstrated robust antibody and T-cell responses that tended to be numerically higher after immunization with monovalent XBB.1.5 rS compared to the bivalent Prototype rS + XBB.1.5 rS formulation.

An additional non-clinical study (702-207) found SARS-CoV-2 JN.1 to be immunogenic in mice as a two-dose primary series and a single two-month booster dose, eliciting superior cross-neutralizing functional antibody responses against JN.1 sublineage variants compared to administration of a booster with XBB.1.5 rS, notably against JN.1, JN.1.11.1, and JN.1.7. These data support a COVID-19 vaccine strain change to JN.1 rS to generate neutralizing antibody responses against forward-drifted SARS-CoV-2 variants, including JN.1.13.1, KQ.1, KP.2, KP.1.1, KP.3, and LA.2.

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			
702-091 57-day repeat-dose Good laboratory practice (GLP) toxicity study of SARS-CoV-2 rS with Matrix-M Adjuvant (Complete)	NZW rabbits (n = 30/group)	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. Effects on clinical pathology parameters (fibrinogen, CRP, and/or globulin), which resolved during the recovery interval, and histopathology (subacute inflammation at injection sites and adjacent tissue), which were decreased at the recovery interval, were consistent with immune stimulation following administration of a vaccine. Anti-S IgG results confirmed vaccine delivery and demonstrated 100% seroconversion.	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.

Table SII.1: Non-Clinical Toxicology Studies

Study Number & Description (Status)	Animals (N)	Key Conclusions	Results Relevant to Human Use
Genotoxicity			
20#312 Non-GLP bacterial reverse mutation assay (Complete)	Not applicable	Matrix-M adjuvant at concentrations up to 1000 µg per plate was negative (non-mutagenic).	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.
20#313 Non-GLP mammalian chromosome aberration assay (Complete)	Not applicable	Matrix-M adjuvant at concentrations up to 100 µg/mL was negative with no significant increases observed for the induction of micronuclei.	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.
20#316 GLP bacterial reverse mutation assay (Complete)	Not applicable	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.	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.
20#317 GLP mammalian cell micronucleus assay (Complete)	Not applicable	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.	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.

Table SII.1: Non-Clinical Toxicology Studies

Study Number & Description (Status)	Animals (N)	Key Conclusions	Results Relevant to Human Use
Reproductive toxicity			
702-096-PILOT Immune response (Complete)	Sprague Dawley rat (n= 4/sex/group)	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.	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.
702-096 GLP developmental and reproductive toxicity study of SARS-CoV-2 rS (Complete)	Sprague Dawley rat (n = 50/sex/group)	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. In the uterine cohort, there was no difference between foetal body weights, survival, or foetal external, visceral, or skeletal exams. In the developmental cohort, there were no differences in number of male and female pups, pup body weights, survival, litter size and sex, developmental markers, or gross pathology findings. SARS-CoV-2 rS with Matrix-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.	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.

Other non-clinical studies

Due to the reassuring safety profile of adjuvanted SARS-CoV-2 Prototype rS in nonclinical toxicology studies, there are no formal toxicology or safety studies planned for the Omicron XBB.1.5 rS and JN.1 rS variant vaccines. However, in pharmacology studies that are either completed or in progress, no informal safety findings have been noted in mice administered monovalent or bivalent XBB.1.5 rS as a two-dose primary series (Study 702-186, 702-188) or after a booster dose (702-191), or in NHPs administered XBB.1.5 rS as a primary series or booster dose (702-173). Similarly, no informal safety findings were reported following a two-dose primary series or booster dose of JN.1 rS in mice and NHPs (702-207, 702-173).

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.

Though not a formal safety study, a mouse biodistribution study (22#330) was undertaken to further understand the disposition of the saponins in Matrix-M adjuvant. Saponins were cleared rapidly from the injection site and iliac nodes, entered the plasma quickly (peaking at 1 hour post injection), and were excreted in urine. Excluding low levels in the liver, spleen, and kidneys (which were all declining at 168 hours post injection), there was no accumulation of saponin in non-lymphoid tissues.

Part II: Module SIII - Clinical Trial Exposure

The following studies are ongoing at the clinical trial DLP of this RMP:

- 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-311 Part 2 (Australia): A Multi-Part, Phase 3, Randomized, Observer Blinded Study to Evaluate the Safety and Immunogenicity of Omicron Subvariant and Bivalent SARS-CoV-2 rS Vaccines 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 studies were 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.*
- 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 Participants. *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. Data from this study will be included in a future EU RMP update comprised of recently completed CSRs.*
- 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. *Data from this study will be included in a future EU RMP update comprised of recently completed CSRs.*
- 2019nCoV-311 Part 1 (Australia): A 2-Part, Phase 3, Randomized, Observer Blinded Study to Evaluate the Safety and Immunogenicity of Omicron Subvariant and Bivalent SARS-CoV-2 rS Vaccines in Adults Previously Vaccinated with Other COVID-19 Vaccines. *Data from this study will be included in a future EU RMP update comprised of recently completed CSRs.*

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-301, and 2019nCoV-501.

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.16, Table SIII.17, and Table SIII.18 present exposure of adult participants ≥ 18 years of age who were administered one heterologous booster dose (2019nCoV-311 Part 1) or two heterologous booster doses (2019nCoV-311 Part 2).

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	1771	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	1,878	0	0	1,898
301	16	9	12,734	17	1	12,777
Total	**16**	**29**	**14,717**	**17**	**1**	**14,780**

*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**

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

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

Table SIII.16 and Table SIII.17 present exposure data for 2019nCoV-311 Part 1 Groups C, D, and E (i.e., participants previously vaccinated with 3 doses of Moderna and/or Pfizer-BioNTech prototype COVID-19 vaccines); participants enrolled in Groups A and B will be included in exposure data at a future time as Part 1 of the study remains ongoing. Table SIII.16 and Table SIII.18 present data from

2019nCoV-311 Part 2 Groups F, G, and H (participants previously vaccinated with ≥ 3 doses of Moderna and/or Pfizer-BioNTech monovalent and/or bivalent COVID-19 vaccines).

Table SIII.16: Exposure in Adult Participants (≥ 18 Years of Age) from 2019nCoV-311 Part 1 and Part 2

Group	Previous COVID-19 Vaccines	Novavax COVID-19 Vaccine Booster (antigen/Matrix-M adjuvant)	Total Participants (Safety Analysis Set)
C	3 doses Moderna and/or Pfizer-BioNTech	1 dose of NVX-CoV2515 (5 µg/50 µg)	286
D		1 dose of NVX-CoV2373 (5 µg/50 µg)	274
E	3 doses Moderna and/or Pfizer-BioNTech	1 dose of Bivalent NVX-CoV2373 + NVX-CoV2515 (5 µg/50 µg [total])	269
	Total		**829**
F	≥ 3 doses of Moderna and/or Pfizer-BioNTech monovalent and/or bivalent COVID-19 vaccines	2 doses of NVX-CoV2540 (5 µg/50 µg)	254
G		2 doses of NVX-CoV2373 (5 µg/50 µg)	251
H		2 doses of bivalent NVX-CoV2373 + NVX-CoV2540 (5 µg/50 µg [total])	259
	Total		**764**

Table SIII.17: Exposure by Age, Gender, Race, and Ethnicity in Adult Participants (≥ 18 Years of Age) in Clinical Study 2019nCoV-311 Part 1 (Safety Analysis Set)

Parameters	Group C NVX-CoV2515 N = 286	Group D NVX-CoV2373 N = 274	Group E Bivalent (NVX-CoV2373 + NVX-CoV2515) N = 269
Age (years)			
Mean (SD)	40.4 (12.14)	40.1 (11.51)	39.9 (12.35)
Median	42.0	41.0	41.0
Min – max	18 – 64	18 – 64	18 – 64
Sex, n			
Male	133	131	118
Female	153	143	151
Race, n			
White	233	215	220
Black or African American	0	2	0
Aboriginal Australian	2	1	2
Native Hawaiian or Other Pacific Islander	1	0	1
Asian	37	45	39
Mixed Origin	5	3	1
Other	8	8	6
Not Reported	0	0	0

Table SIII.17: Exposure by Age, Gender, Race, and Ethnicity in Adult Participants (≥ 18 Years of Age) in Clinical Study 2019nCoV-311 Part 1 (Safety Analysis Set)

Parameters	Group C NVX-CoV2515 N = 286	Group D NVX-CoV2373 N = 274	Group E Bivalent (NVX-CoV2373 + NVX-CoV2515) N = 269
Ethnicity, n			
Australian	252	236	233
Aboriginal/Torres Strait Islanders	4	3	2
Hispanic or Latino	6	8	6
Not reported	12	15	17
Unknown	10	11	9
Missing	2	1	2
Regimen of previous COVID-19 vaccine,			
Moderna	0	2	5
Pfizer-BioNTech	213	214	200
Mixed	73	58	64
Moderna-Moderna-Pfizer	1	1	0
Moderna-Pfizer-Pfizer	2	0	1
Moderna-Pfizer-Moderna	0	0	0
Pfizer-Pfizer-Moderna	70	56	63
Pfizer-Moderna-Moderna	0	1	0
Pfizer-Moderna-Pfizer	0	0	0

Abbreviations: COVID-19 = coronavirus disease 2019; max = maximum; min = minimum; NVX-CoV2515 = 5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant; NVX-CoV2373 = 5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant; NVX-CoV2373 + NVX-CoV2515 = 5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant (total);

Note: Age was calculated at the time of informed consent.

Note: n for continuous parameters represents the number of participants with non-missing values for that parameter.

Source: 2019nCoV-311 Part 1 interim clinical study report (CSR) Table 9; T14.1.5.2

Table SIII.18: Exposure by Age, Gender, Race, and Ethnicity in Adult Participants (≥ 18 Years of Age) in Clinical Study 2019nCoV-311 Part 2 (Safety Analysis Set)

Parameters	Group F NVX-CoV2540 (N=254)	Group G NVX-CoV2373 (N=251)	Group H Bivalent NVX-CoV2373 + NVX-CoV2540 (N=259)
Age (years)			
Mean (SD)	41.8 (12.89)	41.9 (13.58)	42.4 (12.48)
Median	43.0	43.0	43.0
Min – max	18 – 75	18 – 83	18 – 71

Table SIII.18: Exposure by Age, Gender, Race, and Ethnicity in Adult Participants (≥ 18 Years of Age) in Clinical Study 2019nCoV-311 Part 2 (Safety Analysis Set)

Parameters	Group F NVX-CoV2540 (N=254)	Group G NVX-CoV2373 (N=251)	Group H Bivalent NVX-CoV2373 + NVX-CoV2540 (N=259)
Age (years) Category, n			
18 to 54	211	209	212
≥ 55	43	42	47
Sex, n			
Male	113	111	120
Female	141	140	139
Race, n			
White	195	205	215
Black or African American	1	1	0
Aboriginal Australian	4	3	8
Native Hawaiian or Other Pacific Islander	2	2	1
Asian	36	32	26
Mixed Origin	6	0	1
Other	10	8	6
Not Reported	0	0	2
Ethnicity, n			
Australian	220	221	224
Aboriginal/Torres Strait Islanders	5	5	7
Hispanic or Latino	5	3	8
Not reported	13	13	11
Unknown	11	8	7
Missing	0	1	2
Regimen of Previous COVID-19 Vaccine, n			
3 doses	138	147	149
3 Moderna	5	1	2
3 Pfizer-BioNTech	108	109	121
1 Moderna + 2 Pfizer-BioNTech	24	36	26
2 Moderna + 1 Pfizer-BioNTech	1	1	0
4 doses	116	99	107
4 Moderna	0	1	0
4 Pfizer-BioNTech	72	53	66
1 Moderna + 3 Pfizer-BioNTech	33	28	24
2 Moderna + 2 Pfizer-BioNTech	11	17	17
3 Moderna + 1 Pfizer-BioNTech	0	0	0

Table SIII.18: Exposure by Age, Gender, Race, and Ethnicity in Adult Participants (≥ 18 Years of Age) in Clinical Study 2019nCoV-311 Part 2 (Safety Analysis Set)

Parameters	Group F NVX-CoV2540 (N=254)	Group G NVX-CoV2373 (N=251)	Group H Bivalent NVX-CoV2373 + NVX-CoV2540 (N=259)
5 doses	0	5	3
5 Moderna	0	0	0
5 Pfizer-BioNTech	0	4	2
1 Moderna + 4 Pfizer-BioNTech	0	1	1
2 Moderna + 3 Pfizer-BioNTech	0	0	0
3 Moderna + 2 Pfizer-BioNTech	0	0	0
4 Moderna + 1 Pfizer-BioNTech	0	0	0

Abbreviations: COVID-19 = coronavirus disease 2019; max = maximum; min = minimum; NVX-CoV2540 = 5 µg SARS-CoV-2 rS Omicron BA.5 subvariant with 50 µg Matrix-M adjuvant; NVX-CoV-2373 = 5 µg SARS-CoV-2 rS prototype Wuhan strain with 50 µg Matrix-M adjuvant; NVX-CoV2373 + NVX-CoV2540 = 5 µg SARS-CoV2 rS with 50 µg Matrix-M adjuvant (total); SD = standard deviation.

Note: Age was calculated at the time of informed consent.

Note: n for continuous parameters represents the number of participants with non-missing values for that parameter.

Source: 2019nCoV-311 Part 2 Table 8, T14.1.5.2

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.
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	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.

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)
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	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)
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. 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) Received influenza vaccination or any other adult vaccine within 4 days prior to or within 7 days after either study vaccination (Study 301)	Allowance of this condition would confound assessment of safety and efficacy.	Yes	Not applicable; interaction with other vaccines is included as missing information.
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)	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.	No	While participants requiring oxygen therapy were excluded, participants with stable COPD and other pulmonary diseases were included.
Paediatric participants < 12 years of age	Clinical development programmes generally investigate first the benefit-risk in adults. In adults, the risk of symptomatic and severe COVID-19 usually seems higher.	No	A paediatric investigation plan has been agreed with the Agency on 15 October 2021.

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.

Study2019nCoV-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 while study 2019nCoV-101 (Part 2) evaluated the safety and immunogenicity of booster dose of administered to adults approximately 6 and 12 months after the primary vaccination series. Safety and immunogenicity data are available for both studies. 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 immunisation.

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 Nuvaxovid/Nuvaxovid XBB.1.5/Nuvaxovid JN.1 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/ Nuvaxovid XBB.1.5/Nuvaxovid JN.1 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, Table SIII.15, Table SIII.17, and Table SIII.18 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 either conditional/emergency use authorisation or full marketing authorisation approval in multiple countries and regions in collaboration with partners. Please refer to Periodic Benefit Risk Evaluation Report (PBRER) no.3 (DLP 19 December 2023) 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 (SIIPL).

Cumulative distribution and administration data as of 19 December 2023 are provided below in Table SV.1.2 by country and/or region and strain.

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

Region/License Partner (LP)	Nuvaxovid		Nuvaxovid XBB.1.5	
	Total Doses Administered	Total Doses Distributed	Total Doses Administered	Total Doses Distributed
Australia (Biocelect Pty Ltd.)[a]	271,660	27,384,300	0	0
Canada (NVX)[a]	36,108	9,749,000	0	0
EU (NVX)[a]	355,804	23,733,070	Not available	1,398,000
Germany (NVX) [a]	160,154	24,986,210	Not available	1,581,520
India (SIIPL)[b]	53,355	126,250	0	0
Indonesia (SIIPL)[b]	Not available	9,008,000	0	0
Israel (Medicalix/Freyr)[a]	43	1,535,100	0	0
Japan (Takeda)[a]	348,524	8,238,590	0	0
New Zealand (Biocelect New Zealand Ltd.)[a]	7,867	2,283,800	0	0
Singapore (PharmEng Technology Pte Ltd)[a]	40,873	705,000	0	0
South Korea (SK Bioscience)[a]	974,405	2,932,470	Not available	50,400
Switzerland (NVX)[a]	3,073	526,400	0	0
Taiwan (NVX)[a]	640,584	1,805,200	0	0
Thailand (SIIPL)[b]	Not available	200,000	0	0
UK (NVX)[a]	1,267	1,000,000	0	0
USA (NVX)[a]	89,195	4,737,800	152,894	1,227,690
Novavax/ Nuvaxovid total	**2,929,577**	**106,637,420**	152,894	**4,257,610**
COVOVAX total	**53,355**	**9,334,250**	**0**	**0**
Cumulative total	**2,982,912**	**115,971,670**	152,894	**4,257,610**

[a] Distributed as Novavax/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 in the initial 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 and NVX-CoV2601 is described below for local and systemic reactions.

Nuvaxovid (Original, Wuhan strain)

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 (≥ 1/10) occurring ADRs following IM injection of NVX-CoV2373. Injection site redness/injection site erythema and injection site swelling were commonly reported (≥ 1/100 to < 1/10) following IM injection. Injection site pruritus was uncommonly reported (≥ 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 (≥ 1/10). Pyrexia, and pain in extremity were observed as commonly reported (≥ 1/100 to < 1/10) ADRs in clinical studies. Pruritus, rash, lymphadenopathy, erythema, urticaria, hypertension, and chills were uncommonly reported (≥ 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.

Adolescents 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

The safety and immunogenicity of a booster dose of Nuvaxovid was evaluated in an ongoing Phase 3, multicenter, randomised, observer-blinded, placebo-controlled study (2019nCoV-301). Overall, 12,777 participants received a booster dose of the vaccine at least 6 months after the two-dose primary series (median of 11 months between completion of primary series and booster dose). Of the 12,777 participants who received a booster dose, 39 participants did not receive Nuvaxovid for all three doses. 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 tenderness (73%), injection site pain (61%), fatigue (52%), muscle pain (51%), headache (45%), malaise (40%), and joint pain (26%).

Adolescents 12 through 17 years of age

The safety of a booster dose of Nuvaxovid was evaluated in an interim analysis of an ongoing, Phase 3 study (Study 2019nCoV-301). A total of 1,499 participants received a booster dose approximately 9 months after receiving Dose 2 of the primary series. A subset of 220 participants who received the booster dose were evaluated for solicited adverse reactions within 7 days after the booster dose (Ad Hoc Booster Safety Analysis Set), of whom 190 completed the electronic diary.

Solicited adverse reactions occurred at higher frequencies and with higher grade in adolescents compared to adults. The most frequent solicited adverse reactions were injection site tenderness (72%), headache (68%), fatigue (66%), injection site pain (64%), muscle pain (62%), malaise (47%), and nausea/vomiting (26%) with a median duration of 1 to 2 days following vaccination. No new safety concerns from the time of booster dose administration through 28 days after administration were noted among participants.

Nuvaxovid XBB.1.5 (Omicron-adapted Nuvaxovid)

The safety of Nuvaxovid XBB.1.5 is inferred from the safety data of the Nuvaxovid (Original, Wuhan strain) vaccine and the safety data from the adapted Omicron BA.5 vaccine. A booster dose of Nuvaxovid monovalent Omicron BA.5 and bivalent Original/Omicron BA.5 vaccines were evaluated in an ongoing Phase 3 study in participants 18 years of age and older (2019nCoV-311 Part 2). In this study, 251 participants received a Nuvaxovid (Original, Wuhan strain) booster dose, 254 received a monovalent Omicron BA.5 booster dose, and 259 participants received a Nuvaxovid bivalent Original/Omicron BA.5 booster dose. Median follow-up time since the initial booster vaccination was 48 days through the data cutoff date of 31 May 2023.

The overall safety profile for the Nuvaxovid monovalent Omicron BA.5 booster doses was similar to that seen after the Nuvaxovid (Original, Wuhan strain) booster dose. The most frequent adverse reactions were injection site tenderness (> 50%), injection site pain (> 30%), fatigue (> 30%), headache (> 20%), myalgia (> 20%), and malaise (> 10%). No new adverse reactions were identified for the Nuvaxovid monovalent Omicron BA.5 booster doses. In 2019nCoV-311 Part 2 the frequency of local as well as systemic reactogenicity events was greater in women than in men, for all the vaccine constructs that were tested.

Nuvaxovid JN.1 (Omicron-adapted Nuvaxovid)

The safety of Nuvaxovid JN.1 is inferred from the safety data of the Nuvaxovid (Original, Wuhan strain) vaccine and the safety data from the adapted Omicron BA.5 vaccine. A booster dose of Nuvaxovid monovalent Omicron BA.5 and bivalent Original/Omicron BA.5 vaccines were evaluated in an ongoing Phase 3 study in participants 18 years of age and older (2019nCoV-311 Part 2). In this study, 251 participants received a Nuvaxovid (Original, Wuhan strain) booster dose, 254 received a monovalent Omicron BA.5 booster dose, and 259 participants received a Nuvaxovid bivalent Original/Omicron BA.5 booster dose. Median follow-up time since the initial booster vaccination was 48 days through the data cutoff date of 31 May 2023.

The overall safety profile for the Nuvaxovid monovalent BA.5 booster doses was similar to that seen after the Nuvaxovid (Original, Wuhan strain) booster dose. The most frequent adverse reactions were injection site tenderness (> 50%), injection site pain (> 30%), fatigue (> 30%), headache (> 20%),

myalgia (> 20%), and malaise (> 10%). No new adverse reactions were identified for the Nuvaxovid monovalent Omicron BA.5 booster doses. In 2019nCoV-311 Part 2 the frequency of local as well as systemic reactogenicity events was greater in women than in men, for all the vaccine constructs that were tested.

Aspects of the formulation

Adjuvant:

NVX-CoV2373 with Matrix-M adjuvant is currently being evaluated in 7 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 µg 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/NVX-CoV2601 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 the safety pool for up to 6 months (Study 2019nCoV-505), 8 to 9 months (Study 2019nCoV-311 Part 1 and Study 2019nCoV-311 Part 2, respectively), 1 year post-vaccination (Studies 2019nCoV-101 Part 1 and 2, -501, and -302) or 2 years post-vaccination (Study 2019nCoV-301). In planned clinical studies 2019nCoV-313 and -314 using NVX-CoV2601, participants will be followed for 180 days following vaccination. 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/Nuvaxovid XBB.1.5/Nuvaxovid JN.1 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/Nuvaxovid XBB.1.5/Nuvaxovid JN.1. Instructions on vaccination scheme are provided in SmPC section 4.2. The dose of 0.5 mL is consistent for all vaccine recipients.
- Medical information contact centers are available for the public and HCPs to respond to medical information inquiries about Nuvaxovid/Nuvaxovid XBB.1.5/Nuvaxovid JN.1.
- A website (www.NovavaxCovidVaccine.com) is in place for more information.
- Vaccination record 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 Nuvaxovid/Nuvaxovid XBB.1.5/Nuvaxovid JN.1, 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 Nuvaxovid/Nuvaxovid XBB.1.5/Nuvaxovid JN.1 in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to fertility, pregnancy, embryo/foetal development, parturition, or post-natal development. Administration of Nuvaxovid/Nuvaxovid XBB.1.5/Nuvaxovid JN.1 in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and foetus. It is unknown whether Nuvaxovid/Nuvaxovid XBB.1.5/Nuvaxovid JN.1 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/Nuvaxovid XBB.1.5/Nuvaxovid JN.1 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 Nuvaxovid/Nuvaxovid XBB.1.5/Nuvaxovid JN.1 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 Nuvaxovid/Nuvaxovid XBB.1.5/Nuvaxovid JN.1 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 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 inactivated 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 clinical development programme, understanding of the long-term safety profile of NVX-CoV2373/NVX-CoV2601/NVX-CoV2705 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)	A mechanism of action by which a vaccine could cause myocarditis and/or pericarditis has not been established. 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). 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).
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	**Clinical trial experience (NVX-CoV2373, NVX-CoV2515 (BA.1), NVX-CoV2540 (BA.5))** *Participants 12 years of age and older* 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 including an adolescent participant. 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. 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. As of 04 August 2023, there were no participants who reported a TEAE of myocarditis/pericarditis. **Post-marketing experience (Nuvaxovid (Original, Wuhan strain))** 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 130 ICSRs of myocarditis and/or pericarditis cumulatively as of 19 December 2023 in 57 males and 73 females, age range 18-83 years, when reported). The 130 cumulative ICSRs included 163 AEs, of which 129 were serious. Of these 130 ICSRs, 50 met Level 1- 3 Brighton Collaboration case definitions for myocarditis and/or pericarditis. In the 41 cases where time to onset (TTO) was described, 25 events occurred within 0-7 days of vaccination, 9 within 8-14 days, and 7 within ≥ 15 days; TTO was unknown in 9 cases. Event outcomes in the initial case reports were as follows: Unknown: 25, Recovered/Resolved: 11, Recovered with Sequalae: 2, Recovering/Resolving: 14, Not Recovered/Not Resolved: 29, Fatal: 0. Forty of 50 cases met the case seriousness criteria of Medically Significant, 14 hospitalisation, 1 life-threatening, and 0 fatal. A disproportionate number of cases, 29 (59.6%), were reported from Australia where active surveillance programmes are in place. Risk characterisation will continue to be evaluated as post-marketing data are received. **Post-marketing experience (Nuvaxovid XBB.1.5)** Cumulatively, as of 19 December 2023, 4 ICSRs were retrieved (4 males, age range 14-76 years, when reported) which included 6 AEs of which 2 were serious (medically significant). Of the 4 ICSRs, none met the Level 1 – 3 Brighton Collaboration case definitions for myocarditis and/or pericarditis.

Table SVII.3.1.1: Myocarditis and/or Pericarditis

Important identified risk: Myocarditis and/or pericarditis	
Risk factors and risk groups	Adolescent and young adult males following the second dose of vaccine may be at higher risk (ERVISS 2024 European Respiratory Virus Surveillance Summary (ERVISS). WHO European Region Summary, Week 14/2024 (1-7 April 2024). Available at: https://erviss.org/. Accessed 15 April 2024. 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, and post-market safety data. 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 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).

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)	
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. **Clinical trial experience (NVX-CoV2373, NVX-CoV2515 (BA.1), NVX-CoV2540 (BA.5))** *Participants 18 years of age and older* No events of VAED/VAERD have been reported in adult participants in the clinical development programme and in fact the vaccine has been shown to prevent severe illness. *Participants 12 to < 18 years of age* No events of VAED/VAERD have been reported in participants 12 to < 18 years of age in the clinical development program. **Post-marketing experience (Nuvaxovid (Original, Wuhan Strain))** As of 19 December 2023, there were 7 ICSRs reported of VAED (including VAERD) according to the prescribed search strategy (PTs: Antibody-dependent enhancement; Enhanced respiratory disease). The cases involved 6 males and 1 female, 33 – 71 years of age). All cases were reported from South Korea. The 7 cases were considered to be medically significant by convention, based on IME criteria, however, these cases did not meet the BC level 1 – 3 criteria for VAED/VAERD. As there was insufficient case information to make a causal assessment, Novavax causality was considered indeterminate. **Post-marketing experience (Nuvaxovid XBB.1.5)** Cumulatively, as of 19 December 2023, no initial or follow-up ICSR was retrieved of VAED (including VAERD) according to the prescribed search strategy (PTs: Antibody-dependent enhancement; Enhanced 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 into this, should any VAED occur.
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 in relation to NVX-CoV2373/NVX-CoV2601 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 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/Nuvaxovid XBB.1.5/Nuvaxovid JN.1 in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and foetus. It is unknown whether Nuvaxovid/Nuvaxovid XBB.1.5/Nuvaxovid JN.1 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/Nuvaxovid XBB.1.5/Nuvaxovid JN.1 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/NVX-CoV2601 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, diabetes mellitus (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/NVX-CoV2601 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 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 concurrently administered an inactivated 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. Concomitant administration of Nuvaxovid XBB.1.5 and Nuvaxovid JN.1 with other vaccines has not been studied.
Population in need of further characterisation	Individuals who will receive other vaccines within 28 days prior to or 14 days after immunisation with Nuvaxovid, Nuvaxovid XBB.1.5, and Nuvaxovid JN.1.
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/NVX-CoV2601/NVX-CoV2705 is currently limited. Follow-up in clinical trials is planned to range from 6 – 24 months following vaccinations. The maximum follow-up in clinical studies post dose 2 will be 24 months.
Population in need of further characterisation	Individuals receiving Nuvaxovid, Nuvaxovid XBB.1.5, and Nuvaxovid JN.1.
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	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, review and reporting on aggregate data, and a signal detection and management system.

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 and stakeholders, as appropriate, in accordance with international principles and prevailing regulations.

Signal detection activities

Surveillance is conducted for Nuvaxovid under EMA's GVP framework in accordance with GVP Module IX, Signal Management, the Consideration on core requirements for RMPs of COVID-19 vaccines, the Guideline on good pharmacovigilance practices (GVP) Product- or Population-Specific Considerations I: Vaccines for prophylaxis against infectious diseases, and the Nuvaxovid post-authorisation surveillance plan.

Post-authorisation surveillance and signal detection activities involve both qualitative and quantitative methods. 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), lot reviews, and trend analyses. Safety observations identified for possible validation undergo a preliminary review, and, if validated, a comprehensive evaluation of available data is performed.

Adverse events of special interest have been identified prospectively for close monitoring. Those potential adverse reactions following immunization with established case definitions and background rates undergo observed-to-expected analyses to support signal generation. Signals that reach statistical significance are validated and prioritized for complete evaluation of available data. Results of signal evaluations, including actions taken, if any, are summarized in aggregate reports.

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 record cards (Annex 7) are available to member states for printing if requested and are posted at www.novavaxcovidvaccine.com for download by HCPs at the time of vaccination. The vaccination record 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 other doses of the vaccine as applicable;
- Placeholder spaces for the other doses of the vaccine (as applicable) including the name of the vaccine/manufacturer of the vaccine, batch number, and date of the second dose of the vaccine;
- Novavax website and QR code that links to NovavaxCovidVaccine.com; and
- Information on AE reporting to the member state local health authorities.

In addition to the vaccination record cards, traceability labels (two labels per dose) containing product identifier (brand name), strain, 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 record 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 record 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 are listed below:

Specific adverse reaction follow-up questionnaires associated with an important safety concern:*

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

*Specific adverse reaction follow-up questionnaires not associated with an important safety concern**:*

- Anaphylaxis
- Guillain-Barré Syndrome

*An important safety concern is defined as those risks that are likely to have an impact on the risk-benefit balance of the product. Important risks would usually warrant further evaluation as part of a pharmacovigilance plan and risk minimisation activities (specific clinical actions to be taken to minimize the risk or additional risk minimisation activities).

**At the request of EMA, specific adverse reaction follow-up questionnaires for AESIs not considered important safety concerns have been added to the RMP.

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 Nuvaxovid 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 Participants**

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 participants.

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 participants 18 – 59 years of age (Part 1). Healthy adult participants 18 – 84 years of age (Part 2).

Milestones: Interim clinical study report (CSR) for 2019nCoV-101 (Part 1): 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. The final CSR for 2019nCoV-101 (Part 2) was submitted on 22 February 2024. *Data from this study will be included in a future EU RMP update comprised of recently completed CSRs.*

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 1740 kg/m^2 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 submission date: 30 June 2024.

Study short name and title: **2019nCoV-302; A Phase 3, 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 submission date: 31 July 2024.

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: The final CSR was submitted on 25 January 2024. *Data from this study will be included in a future EU RMP update comprised of recently completed CSRs.*

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 August 2021. Submission of the interim CSR for 2019nCoV-301 pediatric expansion study to EMA: 08 March 2022. Final CSR (participants ≥ 18 years of age) estimated submission date: 30 June 2024. Final CSR (participants 12 to < 18 years of age) estimated submission date: 30 September 2024.

Study short name and title: **2019nCoV-311 Part 1; A 2-Part Phase 3, Randomized, Observer Blinded Study to Evaluate the Safety and Immunogenicity of Omicron Subvariant and Bivalent SARS-CoV-2 rS Vaccines in Adults Previously Vaccinated with Other COVID-19 Vaccines**

Rationale and study objectives:

To determine if NVX-CoV2515 induces superior antibody responses to the Omicron BA.1 subvariant compared to the antibody response induced by NVXCoV2373 in participants previously vaccinated with 3 doses of the Moderna and/or Pfizer-BioNTech prototype vaccines.

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 submitted on 04 April 2024. *Data from this study will be included in a future EU RMP update comprised of recently completed CSRs.*

Study short name and title: **2019nCoV-311 Part 2; A Multi-Part Phase 3, Randomized, Observer Blinded Study to Evaluate the Safety and Immunogenicity of Omicron Subvariant and Bivalent SARS-CoV-2 rS Vaccines in Adults Previously Vaccinated with Other COVID-19 Vaccines**

Rationale and study objectives:

To determine if bivalent vaccine (NVX-CoV2373 + NVX-CoV2540) induces superior antibody responses to the Omicron BA.5 subvariant compared to the antibody response induced by NVX-CoV2373 in participants previously vaccinated with ≥ 3 doses of the Moderna and/or Pfizer-BioNTech monovalent and/or bivalent mRNA vaccines.

Study design: Phase 3, Randomised, Observer-Blinded Study

Study population: Medically stable male and nonpregnant females ≥ 18 years of age in Australia who had previously received a regimen of ≥ 3 doses of the Moderna and/or Pfizer/BioNTech monovalent and/or bivalent COVID-19 vaccines ≥ 90 days previously.

Milestones: Final CSR estimated submission date: 30 September 2024.

Study short name and title: **2019nCoV-313; A Phase 2/3 Open-Label Study to Evaluate the Safety and Immunogenicity of a XBB.1.5 (Omicron Subvariant) SARS-CoV-2 rS Vaccine Booster Dose in Previously mRNA COVID-19 Vaccinated and Baseline SARS-CoV-2 Seropositive COVID-19 Vaccine Naïve Participants**

Rationale and study objectives:

The primary objectives for Part I are to determine if the NVX-CoV2601 vaccine booster induces superior antibody responses to the XBB.1.5 Omicron subvariant compared to those of a historical control of NVX-CoV2373 and to determine if the NVX-CoV2601 vaccine booster induces non-inferior SRRs compared to those of a historical control of NVX CoV2373

The primary objectives for Part 2 are to determine if a single dose of NVX-CoV2601 vaccine in SARS-CoV-2 seropositive COVID-19 vaccine naïve participants induces non-inferior SRRs to the XBB.1.5 Omicron subvariant compared to those of a booster dose of NVX-CoV2601 in previously COVD-19 mRNA vaccinated participants and to determine if a single dose of NVX-CoV2601 vaccine in SARS-CoV-2 seropositive COVID-19 vaccine naïve participants induces non-inferior antibody responses to the XBB.1.5 Omicron subvariant compared to a booster dose of NVX-CoV2601 in previously COVD-19 mRNA vaccinated participants.

Study design: A Phase 2/3 Open-Label Study

Study population: Part 1: Medically stable male and nonpregnant females who are ≥ 18 years of age and vaccinated with ≥ 3 doses of the Moderna and/or Pfizer/BioNTech prototype monovalent and/or BA.4/5 containing bivalent COVID-19 vaccines. Participants last mRNA vaccination must have been administered ≥ 90 days prior to study vaccination. Part 2: Medically stable male and nonpregnant females ≥ 18 years of age unvaccinated to SARSCoV-2 with a clinical history of COVID-19-like infection during the previous year.

Milestones: Part 1 final CSR estimated submission date: 31 December 2024. Part 2 final CSR estimated submission date: 31 December 2024.

Study short name and title: **2019nCoV-314; A Phase 3, Randomized, Double-Blinded Study to Evaluate the Safety and Immunogenicity of Omicron Subvariant and Bivalent SARS-CoV-2 rS Vaccines in Adolescents Previously Vaccinated with mRNA COVID-19 Vaccines**

Rationale and study objectives: Assess the safety and immunogenicity of the Novavax Omicron XBB.1.5 subvariant vaccine (NVX-CoV2601) alone or in combination with the prototype Novavax vaccine (NVX-CoV2373) as a bivalent product in adolescent participants ≥ 12 to < 18 years of age who previously received ≥ 2 doses of approved/authorized monovalent and/or bivalent mRNA vaccines.

Study design: Phase 3, Randomized, Double-Blinded Study

Study population: Medically stable male and nonpregnant female adolescents ≥ 12 to ≥ 18 years of age. All participants will have received a regimen of ≥ 2 doses of the Moderna and/or Pfizer BioNTech COVID-19 monovalent and/or bivalent vaccines ≥ 90 days prior to study vaccination.

Milestones: Final CSR estimated date: 31 December 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 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) an SCCS to compare the incidence of AESIs during pre-specified risk windows following Nuvaxovid vaccination with the incidence during post-vaccination control windows 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 of individuals ≥12 years of age 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. Revised protocols were submitted on 30 September 2022, 29 March 2023, and 05 December 2023.

The first interim report was submitted on 26 June 2023. A revised first interim report was submitted on 05 December 2023. A second interim report is planned for submission by 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 study protocol was submitted on 31 March 2022. A revised protocol was submitted 06 October 2023.

The first interim report was submitted on 19 June 2023. Additional interim reports are planned for submission by 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 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) an SCCS to compare the incidence of select AESIs during pre-specified risk windows following vaccination with the Novavax COVID-19 Vaccine, Adjuvanted with the incidence during post-vaccination control windows 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 of individuals ≥ 12 years of age included in the HealthVerity insurance claims database 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.

Milestones: The draft study protocol was submitted to EMA on 29 June 2022. Revised protocols were submitted on 28 November 2022 and 18 May 2023. Novavax will provide the updated protocol inclusive of subsequent Nuvaxovid strains at the next regulatory opportunity (e.g., with the next interim report).

An interim report was submitted on 26 September 2023. An additional interim report is planned for submission by 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 revised protocols were submitted on 30 August 2022 and 23 January 2024.

Interim reports were submitted on 30 January 2023, 25 July 2023, and 23 January 2024. An additional interim report is planned for submission by 31 July 2024. A final study report is planned for submission by 30 June 2025.

Study short name and title: **2019nCoV-403 (US Post-authorization effectiveness study using a claims 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 of individuals ≥ 12 years of age included in the HealthVerity insurance claims database 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.

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. Novavax will provide the updated protocol inclusive of subsequent Nuvaxovid strains at the next regulatory opportunity (e.g., with the next interim report).

An interim report was submitted on 22 September 2023. An additional interim report is planned for submission by 30 September 2024. A final study report is planned for submission by 30 September 2025.

III.3 Summary Table of Additional Pharmacovigilance Activities

Ongoing and planned studies are presented below. Completed studies are located in Annex 2 and data from these will be integrated in a future update of the RMP.

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-501 Completed, data analysis 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	30 June 2024

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

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
2019nCoV-302 Completed, data analysis ongoing	• 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.	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	Final CSR	31 July 2024
2019nCoV-311 Part 2 Ongoing	To determine if bivalent vaccine (NVX-CoV2373 + NVX-CoV2540) induces superior antibody responses to the Omicron BA.5 subvariant compared to the antibody response induced by NVX-CoV2373 in participants previously vaccinated with ≥ 3 doses of the Moderna and/or Pfizer-BioNTech monovalent and/or bivalent mRNA vaccines.	Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) Myocarditis and/or pericarditis Long-term safety	Final CSR	30 September 2024

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

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
2019nCoV-301 Ongoing	• 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.	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 (Adults) Final CSR (Adolescents)	30 June 2024 30 September 2024

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

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
2019nCoV-313 Ongoing	**Primary Objectives (Part 1):** 1. To determine if the NVX-CoV2601 vaccine booster induces superior antibody responses to the XBB.1.5 Omicron subvariant compared to those of a historical control of NVX-CoV2373 2. To determine if the NVX-CoV2601 vaccine booster induces non-inferior SRRs compared to those of a historical control of NVX CoV2373 **Primary Objectives (Part 2):** 1. To determine if a single dose of NVX-CoV2601 vaccine in SARS-CoV-2 seropositive COVID-19 vaccine naïve participants induces non-inferior SRRs to the XBB.1.5 Omicron subvariant compared to those of a booster dose of NVX-CoV2601 in previously COVD-19 mRNA vaccinated participants. 2. To determine if a single dose of NVX-CoV2601 vaccine in SARS-CoV-2 seropositive COVID-19 vaccine naïve participants induces non-inferior antibody responses to the XBB.1.5 Omicron subvariant compared to a booster dose of NVX-CoV2601 in previously COVD-19 mRNA vaccinated participants.	Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) Myocarditis and/or pericarditis Long-term safety	Part 1 Final CSR Part 2 Final CSR	31 December 2024 31 December 2024

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

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
2019nCoV-314 Ongoing	Assess the safety and immunogenicity of the Novavax Omicron XBB.1.5 subvariant vaccine (NVX-CoV2601) alone or in combination with the prototype Novavax vaccine (NVX-CoV2373) as a bivalent product in adolescent participants ≥ 12 to < 18 years of age who previously received ≥ 2 doses of approved/authorized monovalent and/or bivalent mRNA vaccines.	Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) Myocarditis and/or pericarditis Long-term safety	Final CSR	31 December 2024
2019nCoV-402 Post-Authorisation Safety Study Using the Clinical Practice Research Datalink (CPRD) Ongoing	To evaluate the risk of select safety outcomes of interest following vaccination with Nuvaxovid using a (i) a self-controlled case series (SCCS) design and (ii) a comparative cohort study design.	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	Interim reports	30 June 2024
			Final study report	30 June 2025

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

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
2019nCoV-405 Global Pregnancy and infant outcomes study using the COVID-19 Vaccines International Pregnancy Exposure Registry Ongoing	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.	Use in pregnancy and while breastfeeding	Interim reports	30 June 2024, 30 June 2025, 30 June 2026
			Final study report	30 June 2027
2019nCoV-404 US Post-authorization safety study using a claims database Ongoing	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.	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	Interim reports	30 September 2024
			Final study report	30 September 2025

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	• 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 and one additional dose of Nuvaxovid compared to 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 2024
			Final report	30 June 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 Database Ongoing	Primary objective: To estimate the effectiveness of the Novavax COVID-19 Vaccine, Adjuvanted in preventing COVID-19 hospitalisations compared to unvaccinated individuals. Secondary objectives: • 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: o after a single dose in reducing clinically defined SARS-CoV-2 infection o against SARS-CoV-2 variants (where data is available) o 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 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	Routine risk communication: SmPC section 4.4 and 4.8. PL section 2 and 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC section 4.4 and PL sections 2 and 4: Recommendation to seek immediate medical attention if symptoms of myocarditis or pericarditis occur. Other routine risk minimisation measures beyond the Product Information: None
Important potential risks	
Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None
Missing information	
Use in pregnancy and while breastfeeding	Routine risk communication: SmPC section 4.6 and 5.3 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None

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

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

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	Routine risk minimisation measures: SmPC section 4.4 and 4.8. PL section 2 and 4. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond ADR reporting and signal detection: *Specific adverse reaction follow-up questionnaire* Additional pharmacovigilance activities: **Ongoing clinical trials** 2019nCoV-501; final CSR estimated date 30 June 2024 2019nCoV-302; final CSR estimated date 31 July 2024 2019nCoV-311 Part 2; final CSR estimated date 30 September 2024 2019nCoV-301; final CSR (Adults) estimated date 30 June 2024; final CSR (Adolescents) estimated date 30 September 2024 2019nCoV-313; Part 1 final CSR estimated date 31 December 2024; Part 2 final CSR estimated date 31 December 2024 2019nCoV-314; final CSR estimated date 31 December 2024 **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 database); final study report estimated date 30 September 2025

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		
Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)	Routine risk minimisation measures: None Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond ADR reporting and signal detection: *Specific adverse reaction follow-up questionnaire* Additional pharmacovigilance activities: **Ongoing clinical trials** 2019nCoV-501; final CSR estimated date 30 June 2024 2019nCoV-302; final CSR estimated date 31 July 2024 2019nCoV-311 Part 2; final CSR estimated date 30 September 2024 2019nCoV-301; final CSR estimated date 30 June 2024; final CSR (Adolescents) estimated date 30 September 2024 2019nCoV-313; final CSR estimated date 31 December 2024; Part 2 final CSR estimated date 31 December 2024 2019nCoV-314; final CSR estimated date 31 December 2024 **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 database); final study report estimated date 30 September 2025
Missing information		
Use in pregnancy and while breastfeeding	Routine risk minimisation measures: SmPC Sections 4.6 and 5.3 PL Section 2 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond ADR reporting and signal detection: None Additional pharmacovigilance activities: **Post-authorisation studies** 2019nCoV-405 (Global Pregnancy and infant outcomes study using the "COVID-19 Vaccines International Pregnancy Exposure Registry" (C-VIPER)); final study report estimated date 30 June 2027

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	Routine risk minimisation measures: SmPC Section 4.4 PL section 2 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond ADR reporting and signal detection: None Additional pharmacovigilance activities: **Ongoing clinical trials** 2019nCoV-501; final CSR estimated date 30 June 2024 2019nCoV-302; final CSR estimated date 31 July 2024 2019nCoV-301; final CSR estimated date 30 June 2024; final CSR (Adolescents) estimated date 30 September 2024 **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 database); final study report estimated date 30 September 2025
Use in frail patients with comorbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)	Routine risk minimisation measures: None Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond ADR reporting and signal detection: None Additional pharmacovigilance activities: **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 database); final study report estimated date 30 September 2025
Use in patients with autoimmune or inflammatory disorders	Routine risk minimisation measures: PL section 2 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond ADR reporting and signal detection: None Additional pharmacovigilance activities: **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 database); final study report estimated date 30 September 2025

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	Routine risk minimisation measures: SmPC Section 4.5 and 5.1 PL section 2 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond ADR reporting and signal detection: None Additional pharmacovigilance activities: **Ongoing clinical trials** 2019nCoV-302; final CSR estimated date 31 July 2024 **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 database); final study report estimated date 30 September 2025
Long-term safety	Routine risk minimisation measures: None Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond ADR reporting and signal detection: None Additional pharmacovigilance activities: **Ongoing clinical trials** 2019nCoV-501; final CSR estimated date 30 June 2024 2019nCoV-302; final CSR estimated date 31 July 2024 2019nCoV-311 Part 2; final CSR estimated date 30 September 2024 2019nCoV-301; final CSR estimated date 30 June 2024; final CSR (Adolescents) estimated date 30 September 2024 2019nCoV-313; final CSR estimated date 31 December 2024; Part 2 final CSR estimated date 31 December 2024 2019nCoV-314; final CSR estimated date 31 December 2024 **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 database); final study report estimated date 30 September 2025

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.

Nuvaxovid is also available as:

- Nuvaxovid XBB.1.5 (Omicron XBB.1.5 subvariant of SARS-CoV-2)
- Nuvaxovid JN.1 (Omicron JN.1 subvariant of SARS-CoV-2)

Further information about the evaluation of Nuvaxovid/Nuvaxovid XBB.1.5/Nuvaxovid JN.1'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 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	Routine risk minimisation measures: SmPC section 4.4 and 4.8. PL section 2 and 4. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Specific adverse reaction follow-up questionnaire* Additional pharmacovigilance activities: **Ongoing clinical trials** 2019nCoV-501; final CSR estimated date 30 June 2024 2019nCoV-302; final CSR estimated date 31 July 2024 2019nCoV-311 Part 2; final CSR estimated date 30 September 2024 2019nCoV-301; final CSR estimated date 30 June 2024; final CSR (Adolescents) estimated date 30 September 2024 2019nCoV-313; final CSR estimated date 31 December 2024; Part 2 final CSR estimated date 31 December 2024 2019nCoV-314; final CSR estimated date 31 December 2024 **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 database); final study report estimated date 30 September 2025

Important potential risk: Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)	
Evidence for linking the risk to the medicine	Literature on viral vaccines, safety information of other COVID-19 vaccines, clinical trials, and post-market safety data. 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 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.
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.
Risk minimisation measures	Routine risk minimisation measures: None Additional risk minimisation measures: None
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Specific adverse reaction follow-up questionnaire* Additional pharmacovigilance activities: **Ongoing clinical trials** 2019nCoV-501; final CSR estimated date 30 June 2024 2019nCoV-302; final CSR estimated date 31 July 2024 2019nCoV-311 Part 2; final CSR estimated date 30 September 2024 2019nCoV-301; final CSR estimated date 30 June 2024; final CSR (Adolescents) estimated date 30 September 2024 2019nCoV-313; final CSR estimated date 31 December 2024; Part 2 final CSR estimated date 31 December 2024 2019nCoV-314; final CSR estimated date 31 December 2024 **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 database); final study report estimated date 30 September 2025

Important missing information: Use in pregnancy and while breastfeeding	
Evidence for linking the risk to the medicine	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/Nuvaxovid XBB.1.5/Nuvaxovid JN.1 in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and foetus. <u>Breastfeeding</u> It is unknown whether Nuvaxovid/Nuvaxovid XBB.1.5/Nuvaxovid JN.1 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 XBB.1.5/Nuvaxovid JN.1 is negligible. <u>Fertility</u> Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.
Risk factors and risk groups	Pregnant and breastfeeding women
Risk minimisation measures	<u>Routine risk communication</u>: SmPC Sections 4.6 and 5.3 PL Section 2 <u>Additional risk minimisation</u>: None
Additional pharmacovigilance activities	<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> None <u>Additional pharmacovigilance activities:</u> 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

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/Nuvaxovid XBB.1.5/Nuvaxovid JN.1 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	Routine risk minimisation measures: SmPC Section 4.4 PL section 2 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: **Ongoing clinical trials** 2019nCoV-501; final CSR estimated date 30 June 2024 2019nCoV-302; final CSR estimated date 31 July 2024 2019nCoV-301; final CSR estimated date 30 June 2024; final CSR (Adolescents) estimated date 30 September 2024 **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 database); final study report estimated date 30 September 2025

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/Nuvaxovid XBB.1.5/Nuvaxovid JN.1 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, diabetes mellitus, cardiovascular disease, chronic kidney disease or HIV).
Risk minimisation measures	Routine risk minimisation measures: None Additional risk minimisation measures: None
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: **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 database); final study report estimated date 30 September 2025

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	Routine risk minimisation measures: PL section 2 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: **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 database); final study report estimated date 30 September 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. Concomitant administration of Nuvaxovid XBB.1.5 and Nuvaxovid JN.1 with other vaccines has not been studied.
Risk factors and risk groups	Individuals who will receive other vaccines within 28 prior to 14 days after immunisation with Nuvaxovid.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.5 and 5.1 PL section 2 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: **Ongoing clinical trials** 2019nCoV-302; final CSR estimated date 31 July 2024 **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 database); final study report estimated date 30 September 2025

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	Routine risk minimisation measures: None Additional risk minimisation measures: None
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: **Ongoing clinical trials** 2019nCoV-501; final CSR estimated date 30 June 2024 2019nCoV-302; final CSR estimated date 31 July 2024 2019nCoV-311 Part 2; final CSR estimated date 30 September 2024 2019nCoV-301; final CSR estimated date 30 June 2024; final CSR (Adolescents) estimated date 30 September 2024 2019nCoV-313; final CSR estimated date 31 December 2024; Part 2 final CSR estimated date 31 December 2024 2019nCoV-314; final CSR estimated date 31 December 2024 **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 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-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-311 Part 2**

Purpose of the study:

To determine if bivalent vaccine (NVX-CoV2373 + NVX-CoV2540) induces superior antibody responses to the Omicron BA.5 subvariant compared to the antibody response induced by NVX-CoV2373 in participants previously vaccinated with ≥ 3 doses of the Moderna and/or Pfizer-BioNTech monovalent and/or bivalent mRNA vaccines.

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-313**

Purpose of the study:

Part 1: Investigate the safety and immunogenicity of the Novavax vaccine variant (XBB.1.5) in previously vaccinated adults to determine if it induces superior antibody responses compared to the authorized prototype vaccine, NVX-CoV2373.

Part 2: Investigate the safety and immunogenicity of 1 dose of NVX-CoV2601 in baseline SARS-CoV-2 seropositive COVID-19 vaccine naïve participants to determine if it induces non-inferior antibody responses compared to a booster dose of NVX-CoV2601 in previously COVID-19 mRNA vaccinated individuals participating in Part 1.

Study: **2019nCoV-314**

Purpose of the study:

Assess the safety and immunogenicity of the Novavax Omicron XBB.1.5 subvariant vaccine (NVX-CoV2601) alone or in combination with the prototype Novavax vaccine (NVX-CoV2373) as a bivalent product in adolescent participants ≥ 12 to < 18 years of age who previously received ≥ 2 doses of approved/authorized monovalent and/or bivalent mRNA vaccines.

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 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 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 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.

Part VII: Annexes

Table Part VII: Annexes

Annex	Table of contents
Annex 4	Specific adverse drug reaction follow-up form examples 4.A: Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) questionnaire 4.B: Myocarditis/pericarditis questionnaire 4.C: Anaphylaxis questionnaire 4.D: Guillain-Barré Syndrome questionnaire
Annex 6	Details of proposed additional risk minimisation activities (if applicable) – Not applicable

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

Specific adverse reaction follow-up questionnaires associated with a safety concern:

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

Annex 4.B: Myocarditis/pericarditis questionnaire

Specific adverse reaction follow-up questionnaires not associated with a safety concern:

Annex 4.C: Anaphylaxis questionnaire

Annex 4.D: Guillain-Barré Syndrome 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	
			☐ Recovered ☐ Event ongoing ☐ Recovering	☐ Resolved with sequelae, *please specify* ☐ Patient died ☐ Unknown
			☐ Recovered ☐ Event ongoing ☐ Recovering	☐ Resolved with sequelae, *please specify* ☐ Patient died ☐ 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**
☐Dyspnea ☐Tachypnea ☐Hypoxemia ☐Cough ☐Cyanosis ☐COVID-19 pneumonia ☐Acute respiratory distress syndrome ☐Lower respiratory tract infection ☐Respiratory failure ☐Pulmonary hemorrhage ☐ Radiographic abnormalities ☐Other:	☐Heart failure ☐Acute cardiac injury ☐Acute myocardial infarction ☐Arrhythmia ☐Pericarditis ☐Myocarditis ☐Cardiogenic shock ☐Other:	☐Coagulopathy ☐ Thrombocytopenia ☐Deep vein thrombosis ☐Disseminated intravascular coagulation ☐Vasculitis ☐Limb ischemia ☐Pulmonary embolism ☐Other:	☐Renal disfunction ☐Acute kidney injury ☐Other:	☐Vomiting ☐Diarrhea ☐Jaundice ☐Abdominal pain ☐Acute liver injury ☒Other:	☐Altered mental status ☐Convulsions/seizures ☐Cranial nerve involvement ☐Encephalopathy ☐Meningitis ☐Cerebrovascular accident ☐Other:	☐Acute arthritis ☐Dermatologic ☐Chilblains ☐Erythema multiforme ☐Multisystem inflammatory syndrome ☐Multiorgan failure *Specify*: ☐Death ☐Other:

7. Relevant Medical History / Concurrent Diseases:

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

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**	
☐ Myocarditis			☐ Recovered ☐ Event ongoing ☐ Recovering	☐ Resolved with sequelae, *please specify* ☐ Patient died ☐ Unknown
☐ Pericarditis			☐ Recovered ☐ Event ongoing ☐ Recovering	☐ Resolved with sequelae, *please specify* ☐ Patient died ☐ 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
						☐ Yes ☐ No
						☐ Yes ☐ No
						☐ Yes ☐ No
						☐ Yes ☐ 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 ☐ Yes ☐ No		
Troponin I ☐ Yes ☐ No		
Creatine Kinase Myocardial ☐ Yes ☐ No		
C-reactive protein ☐ Yes ☐ No		
Erythrocyte sedimentation rate ☐ Yes ☐ No		
D-Dimer ☐ Yes ☐ No		
Cardiac Magnetic Resonance Imaging Study ☐ Yes ☐ No		
Echocardiogram ☐ Yes ☐ No		
EKG ☐ Yes ☐ No		
Radiography ☐ Yes ☐ No		
Myocardial Tissue Histopathology/ Endomyocardial biopsy ☐ Yes ☐ No		
CT scan ☐ Yes ☐ No		
Diagnostic tests for infectious etiologies, including but not limited to COVID-19 ☐ Yes ☐ No		
Other, *pls specify*:		

Thank you for completing this form

ANAPHYLAXIS 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 was not received, was the dose not administered due to the adverse event? ☐ Yes | ☐ No

4.Adverse Event Details:

Adverse Event	Start Date (DD/MM/YY)	Stop Date (DD/MM/YY)	Outcome	
			☐ Recovered ☐ Event ongoing ☐ Recovering	☐ Resolved with sequelae, *please specify* ☐ Patient died ☐ Unknown

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 anaphylaxis? ☐ Yes ☐ No
If yes, please provide the admission and the discharge dates (DD/MM/YY)

Please provide the discharge report information:

Major Criteria (Please check all that apply)
Dermatologic or mucosal
☐ Generalized urticaria (hives) or generalized erythema

☐ Angioedema (Not hereditary angioedema), localized or generalized
☐ Generalized pruritus with skin rash
☐ Others, *please specify:*

Cardiovascular

☐ Measured hypotension Blood pressure value: _____ mmHg
☐ Clinical diagnosis of uncompensated shock, indicated by the combination of at least 3 of the following:
- ☐ *Tachycardia, please document heart rate: _____beats/minute*
- ☐ *Capillary refill time >3 seconds*
- ☐ *Reduced central pulse volume*
- ☐ *Decreased level of consciousness or loss of consciousness*

☐ Others, *please specify:*

Respiratory

☐ Bronchospasm (bilateral wheezing)
☐ Stridor
☐ Upper airway swelling (lip, tongue, throat, uvula, or larynx)
☐ Respiratory distress—2 or more of the following:
- ☐ *Tachypnoea, please document respiratory rate: ____ resp./min*
- ☐ *Increased use of accessory respiratory muscles (sternocleidomastoid, intercostals, etc.)*
- ☐ *Recession*
- ☐ *Cyanosis*
- ☐ *Grunting*

☐ Others, *please specify*:

Minor Criteria (Please check all that apply)

Dermatologic or mucosal:

☐ Generalized pruritus without skin rash ☐ Generalized prickle sensation ☐ Localized injection site urticaria
☐ Red and itchy eyes

Cardiovascular:

☐ Reduced peripheral circulation as indicated by the combination of at least 2 of the following:
- ☐ *Tachycardia (please document heart rate) _____ beats/min*
- ☐ *A capillary refill time of >3 seconds without hypotension*
- ☐ *A decreased level of consciousness*

Respiratory:

☐ Persistent dry cough ☐ Hoarse voice ☐ Difficulty breathing without wheeze or stridor
☐ Sneezing, rhinorrhea ☐ Sensation of throat closure

Physical examination (please specify any additional relevant details about the patient):

5.Patient Treatment:

Therapy	**Start Date** ***(DD/MM/YY)***	**Stop Date** ***(DD/MM/YY)***	**Dose/Any additional information, such as frequency and date**
CPR			
Oxygen			
Intravenous fluid challenge			
Bronchodilators			
Epinephrine			
Corticosteroids			
Antihistamines			
Other (*please specify)*			

6.Other Suspect Drugs:

*(*Please only include other drugs you consider that could be the cause of the adverse event as well and not concomitant medications)

Suspect Drug Name	**Indication**	**Daily Dosage**	**Route**	**Start Date** ***(DD/MM/YY)***	**Stop Date** ***(DD/MM/YY)***	**Was suspect drug withdrawn?**
						☐ Yes ☐ No
						☐ Yes ☐ No
						☐ Yes ☐ No
						☐ Yes ☐ No

If any of the above drugs were withdrawn, did the event(s) resolve after stopping? ☐ No ☐ Yes
Did the event(s) recur after reintroduction? ☐ No ☐ Yes ☐ Not applicable

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. Please include all other vaccinations received within the previous month)

Concomitant Drug Name	**Indication**	**Daily Dosage**	**Route**	**Start Date** *(DD/MM/YY)/unknown*	**Stop Date** *(DD/MM/YY)/unknown*

8.Relevant Medical History/Concurrent Diseases

Medical History		**Start Date** *(DD/MM/YY)/unknown*	**Stop Date** *(DD/MM/YY)/unknown*
History of allergy to vaccines or any other medication	☐ Yes ☐ No		
Asthma	☐ Yes ☐ No		
Eczema	☐ Yes ☐ No		
Urticaria/hives	☐ Yes ☐ No		
Hypotension	☐ Yes ☐ No		
Immunosuppressive disorders	☐ Yes ☐ No		
Food allergies (please specify)	☐ Yes ☐ No		
Pollen	☐ Yes ☐ No		
Family history of allergy	☐ Yes ☐ No		
Other allergies (e.g., dust, dog, cat, mold, etc.) (*please specify)*	☐ Yes ☐ No		

Has the patient previously developed hypersensitivity reaction, acute allergic reaction and anaphylaxis, injections site reaction with vaccines, excipients, or other medications? ☐ Yes ☐ No

If yes, which medications did the patient react to, when was the last reaction and what was the time to onset after medication

Has the patient been treated with antihistamines, prednisone, or other medication for any prior hypersensitivity/anaphylaxis or allergic reaction, events? ☐ Yes ☐ No

If yes, please describe the event and the treatment provided:

9.Lab Test / Diagnostic Procedures:

Please provide and/or attach results of relevant laboratory and diagnostic procedures

Lab Test /Diagnostic Procedure	Date	Results

Thank you for completing this form.

GUILLAIN BARRE SYNDROME (GBS) 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/YY)*:

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**	
☐ Guillain Barre Syndrome (GBS) ❑ Acute inflammatory demyelinating polyneuropathy ❑ Miller-Fisher ❑ Acute motor axonal neuropathy ❑ Acute motor and sensory axonal neuropathy ❑ Bickerstaff brainstem encephalitis			☐ Recovered ☐ Event ongoing ☐ Recovering	☐ Resolved with sequelae (mostly back to normal) *Please specify*_____ ☐ Patient died ☐ Unknown
☐ Other (specify)			☐ Recovered ☐ Event ongoing ☐ Recovering	☐ Resolved with sequelae, *please specify*_____ ☐ Patient died ☐ Unknown

Provide details concerning the following exam findings:

Ventilation status (check)

- ❑ Stable in room air
- ❑ Required non-invasive oxygen support
- ❑ Required intubation and ventilation

Weakness

Present ☐ (specify below) Not present ☐
Unknown ☐

- ❑ Eye exam
  - ❑ Normal
  - ❑ Abnormal (describe)_____
- ❑ Facial/bulbar/neck exam
  - ❑ Normal
  - ❑ Abnormal (describe)_____
- ❑ Speech and swallowing exam
  - ❑ Normal
  - ❑ Abnormal (describe)_____

Extremity weakness

Left Arm	(severe ☐ moderate ☐ mild ☐)
Right Arm	(severe ☐ moderate ☐ mild ☐)
Left leg	(severe ☐ moderate ☐ mild ☐)
Right leg	(severe ☐ moderate ☐ mild ☐)

Deep Tendon Reflexes

	left	right
Knee	❑ Normal ❑ Decreased ❑ Increased ❑ Absent	❑ Normal ❑ Decreased ❑ Increased ❑ Absent
Achilles	❑ Normal ❑ Decreased ❑ Increased ❑ Absent	❑ Normal ❑ Decreased ❑ Increased ❑ Absent
biceps	❑ Normal ❑ Decreased ❑ Increased ❑ Absent	❑ Normal ❑ Decreased ❑ Increased ❑ Absent
triceps	❑ Normal ❑ Decreased ❑ Increased ❑ Absent	❑ Normal ❑ Decreased ❑ Increased ❑ Absent

Clinical course

Ascending limb weakness (weakness in legs that spreads to upper body)	Present ☐ Not present ☐ Unknown ☐
Progressive pattern of weakness	Present ☐ Not present ☐ Unknown ☐
Time from weakness onset to weakness at its worst(nadir).	<12 hours ☐ 12 hours and 28 days ☐ >28days ☐ Unknown ☐
Alternate causes of weakness other than Guillain Barre Syndrome	Yes ☐ No ☐ If yes, please list:_____ _____

Paresthesia (burning, tingling or numbness sensation in the legs, feet, or arms)	Present ☐	Not present ☐	Unknown ☐
Ataxia (difficulty with walking and balance, hand coordination, speech, swallowing, and eye movements)	Present ☐	Not present ☐	Unknown ☐
Altered level of consciousness (not as awake, alert, or able to understand or react normally)	Present ☐	Not present ☐	Unknown ☐
Corticospinal tract signs (extensor plantar responses, spasticity, Increased muscle tone)	Present ☐	Not present ☐	Unknown ☐

5. Patient Treatment:

Treatment name (e.g., intravenous immune globulin or IVIG, plasmapheresis)	Start Date (*DD/MM/YY*)	Stop Date (DD/MM/YY)	Route	Daily dose/ Any additional information

6. Medical History/Concurrent Diseases:

Did the patient have any of the following risk factors prior to developing signs and symptoms:

Risk Factors	Start date	Stop date	Was the patient treated for this condition?
Cancer ☐ Yes ☐ No If yes, please specify:			
Diarrheal illness ☐ Yes ☐ No			
Respiratory illness ☐ Yes ☐ No			
Any recent viral or bacterial infection ☐ Yes ☐ No If yes, please specify:			
Surgical procedure (specify) _____ ☐ Yes ☐ No			
Other precipitating factors (specify) _____ ☐ Yes ☐ No			

Please specify any other medical history:

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
						☐ Yes ☐ No
						☐ Yes ☐ No
						☐ Yes ☐ No
						☐ Yes ☐ 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
Electrophysiologic findings: (Neurophysiologic testing) ☐ Yes ☐ No	Typical for GBS ☐ Normal or sensory abnormalities only ☐ Unknown ☐ Other ☐ _____	
CT scan ☐ Yes ☐ No		N/A
MRI ☐ Yes ☐ No		N/A
Other imaging (xray, ultrasound):		
CSF analyses WBC ☐ Yes ☐ No RBC ☐ Yes ☐ No Protein ☐ Yes ☐ No Glucose ☐ Yes ☐ No		
Autoantibody test (specify) ☐ Yes ☐ No		
Basic metabolic panel ☐ Yes ☐ No		
Complete blood count (CBC) ☐ Yes ☐ No		
Other, *please specify*:		

Were there any other factors that precipitated the event? If yes, please describe:

_____

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

Please provide neurology consult notes, as applicable.
Not applicable ☐ Not available ☐ Available see attached ☐

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

Thank you for completing this form

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

Not applicable