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

Phase 3 Adolescent Study for SARS-CoV-2 rS Variant Vaccines

Investigational Products	Monovalent SARS-CoV-2 Omicron XBB.1.5 subvariant vaccine (NVX-CoV2601). Bivalent prototype (Wuhan-Hu-1) and Omicron XBB.1.5 subvariant vaccine (site-mixed NVX-CoV2373 + NVX-CoV2601).
Protocol Number	2019nCoV-314
Clinical Trial Registry Identifiers	NCT05973006
Version Number	4.0
Version Date	21 August 2023
Version	Amendment 2
Sponsor	Novavax, Inc 21 Firstfield Road Gaithersburg, MD 20878 United States

STATEMENT OF COMPLIANCE

The study will be conducted in compliance with this clinical study protocol, Good Clinical Practices (GCP) as outlined by International Council for Harmonisation (ICH) E6(R2), and all applicable local and national regulatory requirements. Enrollment at any clinical study site may not begin prior to that site receiving approval from the ethics committee of record for the protocol and all materials provided to potential participants.

Any amendments to the protocol or changes to the consent document will be approved before implementation of that amendment. Reconsent of previously enrolled participants may be necessary depending on the nature of the amendment.

The Principal Investigator will ensure that changes to the study plan as defined by this protocol will not be made without prior agreement from the Sponsor and documented approval from the ethics committee of record, unless such a change is necessary to eliminate an immediate hazard to the study participants.

All personnel involved in the conduct of this study have completed Human Subjects Protection and GCP Training as outlined by their governing institution.

SPONSOR'S APPROVAL

Title	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
Protocol Number	2019nCoV-314
Version Number	4.0
Version Date	21 August 2023
Amendment	Amendment 2

The design of this study as outlined by this protocol has been reviewed and approved by the Sponsor's responsible personnel as indicated in the signature table below.

Medical Representative		
Name:	**Title:**	**Signature/Date:**
[redacted]	[redacted]	[redacted]
Clinical Operations Representative		
Name:	**Title:**	**Signature/Date:**
[redacted]	[redacted]	[redacted]

INVESTIGATOR'S AGREEMENT

I have read the protocol, appendices, and accessory materials related to Study 2019nCoV-314 and agree to the following:

- To conduct this study as described by the protocol and any accessory materials.
- To protect the rights, safety, and welfare of the participants under my care.
- To provide oversight to all personnel to whom study activities have been delegated.
- To control all investigational products provided by the Sponsor and maintain records of the disposition of those products.
- To conduct the study in accordance with all applicable local and national regulations, the requirements of the ethics committee of record for my clinical site, and Good Clinical Practices as outlined by ICH E6(R2).
- To obtain approval for the protocol and written materials provided to participants prior to initiating the study at my site.
- To obtain informed consent – and updated consent in the event of new information or amendments – from all participants enrolled at my study site prior to initiating any study-specific procedures or administering investigational products to those participants
- To maintain records of each participant's participation and all data required by the protocol.

Name	**Title**	**Institution**
Signature		**Date**

SUMMARY OF CHANGES

Version 1.0 and Version 2.0 of the protocol were signed and approved internally but were not released externally. The changes to Amendment 1.0 Version 3.0 incorporated in Amendment 2.0 Version 4.0 of the protocol, dated 21 August 2023 are summarized in the table below. Editorial and formatting changes are not included in this summary.

Section Number	Summary of Change	Rationale for Change
Section 1.1 Table 1 Schedule of Events **Section 6.1.2.2 Day 0 – On-site Study Vaccination** **Section 6.1.2.3 Day 28 – In-person/Home Health Care Follow-up Visit (-1 to + 7 Days)** **Section 1 Synopsis Exploratory Objectives and Corresponding Endpoints** **Section 3 Objectives and Endpoints Table 2** **Section 9.2.4.4 Mucosal hACE2 Receptor Binding Inhibition Assay Subset** **9.3.2.3 Analysis of Exploratory Immunogenicity Endpoints**	Specify terminology: SARS-CoV-2 *mucosal IgA-mediated* hACE2 receptor binding inhibition and/or antibody responses in a mucosal *IgA-mediated* hACE2 receptor binding inhibition assay.	Clarify that the hACE2 receptor binding inhibition assay is a mucosal IgA-mediated assay.
Section 6.1.1.2 **Unscheduled Study Visits** **Section 6.1.2.8.2** **Unscheduled Visit due to Suspected COVID-19**	*…must contact the site within 3 days of symptom onset. If possible, the participant should be brought in for an in-person visit to help gather vital signs and do any necessary work up inclusive of physical examination.…Only in situations where the participant cannot come in, should a telehealth visit be planned.* ~~must contact sites within 3 days of symptom onset for an unscheduled telehealth visit due to suspected COVID-19~~.	To clarify that whenever possible an on-site rather than a telehealth visit will be conducted for participants with suspected COVID-19 illness.
Section 7.4.1 **Prohibited Therapies**	Topical tacrolimus and ocular cyclosporine are permitted. ~~Use of inhaled glucocorticoids is prohibited.~~ Rabies immune globulin should be administered if medically indicated.	Reference to prohibited use of inhaled glucocorticoids was removed.

Abbreviations: COVID-19 = coronavirus disease 2019; hACE2 = human angiotensin-converting enzyme 2; IgA = Immunoglobulin A; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
24/7	24 hours 7 days a week
2019nCoV	Novel coronavirus
AE	Adverse event
AESI	Adverse event of special interest
AHA	American Heart Association
ANCA	Anti-neutrophil cytoplasmic antibody
AR	Adverse reaction
BMI	Body mass index
CDC	Centers for Disease Control
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CRO	Clinical research organization
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eDiary	Electronic participant-reported outcome diary application
ELISA	Enzyme-linked immunosorbent assay
EOS	End of study
ER	Emergency room
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMC	Geometric mean concentration
GMEU	Geometric mean ELISA unit
GMFR	Geometric mean fold rise
GMT	Geometric mean titer
GMTR	Geometric mean titer ratio (between groups)
GP	Glycoprotein
hACE2	Human angiotensin-converting enzyme 2
HBV	Hepatitis B virus
HEENT	Head, eyes, ears, nose, and throat
HIV	Human immunodeficiency virus
HPV	Human papilloma virus

Abbreviation	Definition
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
ID_{50}	Inhibitory dilution at a concentration of 50%
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IM	Intramuscular
IMP	Investigational medical product
IND	Investigational New Drug
IRB	Institutional Review Board
IWRS	Interactive Web Response System
LB	Lower bound
LBCI	Lower bound confidence interval
LLOQ	Lower Limit of Quantitation
MAAE	Medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East Respiratory Syndrome
MHC	Major histocompatibility complex
mRNA	Messenger ribonucleic acid
NAb	Neutralizing Antibody
NVX-CoV2373	Prototype vaccine with Matrix-M adjuvant
NVX-CoV2515	Omicron BA.1 subvariant vaccine with Matrix-M adjuvant
NVX-CoV2601	Omicron XBB.1.5 subvariant vaccine with Matrix-M adjuvant
OTC	Over-the-counter
PCR	Polymerase chain reaction
PIMMC	Potential immune-mediated medical conditions
PP	Per-Protocol
PT	Preferred term
r	Recombinant
RNA	Ribonucleic acid
S	Spike (protein)
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Suspected adverse reaction
SARS-CoV	Severe acute respiratory syndrome coronavirus

Abbreviation	Definition
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SARS-CoV-2 rS	Severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine
SCR	Seroconversion rate
Sf9	*Spodoptera frugiperda*
SII	Serum Institute of India
SMC	Safety Monitoring Committee
SOC	System organ class
SOE	Schedule of Events
SOP	Standard operating procedure
Td	Tetanus diphtheria
Tdap/Dtap	Tetanus, diphtheria and pertussis
TEAE	Treatment-emergent adverse event
UK	United Kingdom
US	United States
VOC	Variants of concern
VRBPAC	Vaccines and Related Biological Products Advisory Committee
WHO	World Health Organization

1 SYNOPSIS

Study Title	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
Short Title	Phase 3 Adolescent Study for SARS-CoV-2 rS Variant Vaccines
Study Phase	3
Study Design	This is a Phase 3, randomized, double-blinded study to evaluate the safety and immunogenicity of booster doses of Omicron subvariant severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) recombinant rS spike (S) protein nanoparticle vaccines (SARS-CoV-2 rS) adjuvanted with Matrix-M™ adjuvant (NVX-CoV2601 [Omicron XBB.1.5]) and bivalent (NVX-CoV2373 [prototype] + NVX-CoV2601) in previously vaccinated adolescent participants ≥ 12 to < 18 years of age. Approximately 400 adolescents who have received a regimen of ≥ 2 doses of the Moderna and/or Pfizer-BioNTech monovalent and/or bivalent COVID-19 vaccines ≥ 90 days previously will be randomized 1:1 to Group A or Group B: • Group A: 1 dose of NVX-CoV2601 (1 on Day 0) • Group B: 1 dose of bivalent NVX-CoV2373 + NVX-CoV2601 (1 on Day 0) All participants will remain on study for immunogenicity and safety data collection through Day 180.
Rationale	Novavax, Inc., is developing recombinant vaccines adjuvanted with the saponin based Matrix-M adjuvant for the prevention of disease caused by SARS-CoV-2. Given the widespread circulation of Omicron subvariants, regulatory body discussions, and the associated decreased immunogenicity and efficacy of previously approved vaccines based on the prototype Wuhan strain, vaccines based on the Omicron subvariant XBB.1.5 (NVX-CoV2601) were developed and are being evaluated for safety and immunogenicity. The Omicron subvariant product in this study will also be used in combination with a prototype (Wuhan-Hu-1) NVX-CoV2373 in the form of a site-mixed bivalent vaccine to explore the safety and immunogenicity of vaccines containing antigen for both the ancestral (Wuhan) and XBB.1.5 subvariant strains of SARS-CoV-2. This study is designed to 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. The safety profile of the booster dose will be assessed along with its ability to increase antibody titers against the Omicron XBB.1.5 subvariant. If favorable safety and immunogenicity profiles are observed following the booster dose of NVX-CoV2601 or the bivalent product, this would support the use of bivalent, variant based vaccines in adolescents in the global COVID-19 vaccination effort.
Target Population	Medically stable male and non-pregnant 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.

<table>
<tr><td>Number of Participants</td><td>Approximately 400 participants
<table>
<tr><th>Group</th><th>Previous Vaccine</th><th>Novavax Vaccine Booster (antigen/adjuvant)</th><th>n</th></tr>
<tr><td>A</td><td rowspan="2">≥ 2 doses Moderna and/or Pfizer-BioNTech</td><td>NVX-CoV2601 (5 µg/50 µg)</td><td>200</td></tr>
<tr><td>B</td><td>Bivalent NVX-CoV2373 + NVX-CoV2601 (5 µg/50 µg [total])</td><td>200</td></tr>
</table></td></tr>
<tr><td>Length of Participation</td><td>On study (including screening and follow-up):
Up to approximately 194 days (7 months)</td></tr>
<tr><td>Interventions</td><td>1. NVX-CoV2601 (5 µg): Coformulated Omicron XBB.1.5 SARS-CoV-2 rS vaccine with Matrix-M adjuvant: supplied as a solution for preparation for injection, at a concentration of 10 µg antigen and 100 µg adjuvant per mL. All injections will be administered in a 0.5 mL injection volume at a dose of 5 µg antigen with 50 µg Matrix-M adjuvant.
2. Prototype/XBB.1.5 Bivalent Vaccine (5 µg): A site-mixed bivalent vaccine prepared by combining 0.25 mL of NVX-CoV2373 and 0.25 mL NVX-CoV2601. All injections will be administered in a 0.5 mL injection volume at a dose of 5 µg total antigen (2.5 µg prototype antigen + 2.5 µg Omicron XBB.1.5 antigen) with 50 µg Matrix-M adjuvant.</td></tr>
<tr><td>Primary Safety Objective and Endpoints</td><td>Objective: To assess the overall safety of 1 heterologous booster dose of NVX-CoV2601 and the bivalent vaccine (NVX-CoV2373 + NVX-CoV2601).
Endpoints:
• Incidence, duration, and severity of solicited local and systemic adverse events (AEs) for 7 days following vaccination.
• Incidence, severity, and relationship of unsolicited AEs through 28 days after vaccination
• Incidence and severity of medically attended adverse events (MAAEs) attributed to study vaccine, adverse events of special interest (AESIs) (predefined list including potential immune-mediated medical conditions (PIMMCs), myocarditis and/or pericarditis, and complications specific to COVID-19), and serious adverse events (SAEs) through day 180 or end of study (EOS).</td></tr>
<tr><td>Primary Immunogenicity Objective and Endpoints</td><td>Objective: To describe the neutralizing antibody (NAb) response induced by NVX-CoV2601 and the bivalent vaccine (NVX-CoV2373 + NVX-CoV2601) against the Omicron XBB.1.5 strain.
• Neutralizing antibody (NAb) geometric mean titers (GMTs) to the Omicron XBB.1.5 strain, assessed at Day 28 following initial study vaccination.
• NAb geometric mean fold rise (GMFR) at Day 28 from baseline (Day 0).</td></tr>
<tr><td>Secondary Objectives and Corresponding Endpoints</td><td>Objective: To describe the NAb response induced by NVX-CoV2601 and the bivalent vaccine (NVX-CoV2373 + NVX-CoV2601) against the Omicron XBB.1.5 strain over time.
Endpoints:
• NAb GMTs to the Omicron XBB.1.5 strain at relevant time points (Days 0, 90, and 180).
• NAb GMFR at relevant time points (Days 90, and 180) from baseline (Day 0).</td></tr>
</table>

	Objective: To describe immunoglobulin G (IgG) antibody levels induced by NVX-CoV2601 and the bivalent vaccine (NVX-CoV2373 + NVX-CoV2601) against the Omicron XBB.1.5 strain over time. Endpoints: • IgG geometric mean ELISA (enzyme linked immunosorbent assay) units (GMEUs) to the Omicron XBB.1.5 S protein at relevant time points (Days 0, 28, 90, and 180). Derived/calculated endpoints based on these data will include GMFR.
Exploratory Objectives and Corresponding Endpoints	Objective: To describe the NAb and IgG antibody responses induced by NVX-CoV2601 and the bivalent vaccine (NVX-CoV2373 + NVX-CoV2601) against the ancestral (Wuhan) strain over time. Endpoints: • NAb titers and IgG GMEUs to the ancestral (Wuhan) strain at relevant time points (Days 0, 28, 90, and 180). Derived/calculated endpoints based on these data will include GMFR. Objective: To describe antibody responses in a human angiotensin converting enzyme-2 (hACE2) receptor binding inhibition assay induced by NVX-CoV2601 and the bivalent vaccine (NVX-CoV2373 + NVX-CoV2601) to the Omicron XBB.1.5 and ancestral (Wuhan) strains over time. Endpoints: • GMTs to the Omicron XBB.1.5 and ancestral (Wuhan) strains at relevant time points (Days 0, 28, 90, and 180). Derived/calculated endpoints based on these data will include GMFR. Objective: To describe antibody responses in a mucosal IgA-mediated hACE2 receptor binding inhibition assay induced by NVX-CoV2601 and the bivalent vaccine (NVX-CoV2373 + NVX-CoV2601) to the Omicron XBB.1.5 and ancestral (Wuhan) strains over time. Endpoints: • GMTs to the Omicron XBB.1.5 and ancestral (Wuhan) strains at relevant time points (Days 0 and 28). Derived/calculated endpoints based on these data will include GMFR. Objective: To utilize additional assays (current or to be developed) to better characterize the immune response for future vaccine development needs. Endpoint: Additional endpoints to evaluate immune responses may be developed based on the assays used. Objective: To characterize the severity of COVID-19 in participants who become infected during the course of the study. Endpoint: Detected case will be characterized as mild, moderate, or severe as assessed using the provided criteria.
Number of Sites	Up to 25 sites in the United States and Canada (Canadian sites contingent upon additional approval).
Study Duration	Estimated duration: Approximately 7 months

1.1 Schedule of Events

The schedule of events (SOE) is presented in Table 1.

Table 1: Schedule of Events for Study 2019nCoV-314

Study Day	**–14 to 0[1]**	**0[1]**	**28**	**56**	**90**	**118**	**146**	**180**	**Unscheduled Visit[2, 19]**	
Window (days)[3]			**-1 to + 7**	**± 7**	**± 7**	**± 7**	**± 15**	**± 15**		
Study Visit	**Screening**	**1**	**2[19]**	**3 (Phone)**	**4[19]**	**5 (Phone)**	**6 (Phone)**	**EOS[4, 19]**	**Gen**	**Sp**
Informed consent	X									
Medical history[5]	X									
Inclusion/exclusion criteria[6]	X	X[7]								
Demographics[8]	X									
Prior/concomitant medications[9]	X	X[7]	X	X	X	X	X	X	X	X
Vital sign measurements[10]	X	X[7]						X	X	
Urine pregnancy test (POCBP)[11]	X	X[7]								
Physical examination[12]	X	X[7]			X			X	X	
Baseline ECG		X[7]								
Monitoring and Assessment of COVID-19 Severity[13]			X	X	X	X	X	X		
Nasal swab for SARS-CoV-2 (PCR) – anterior nares		X[7]								X
Oral swab for SARS-CoV-2 (mucosal IgA-mediated hACE2 receptor-binding inhibition assay)		X	X							
Blood sampling for SARS-CoV-2 serostatus (anti N-protein serology)		X[7]	X					X		
Blood sampling for SARS-CoV-2 (ELISA for anti S-protein serology)		X[7]	X		X			X		X
Blood sampling for SARS-CoV-2 NAb assay		X[7]	X		X			X		X
Blood sampling for hACE2 receptor-binding inhibition assay		X[7]	X		X			X		X
Vaccination[14]		X								

Table 1: Schedule of Events for Study 2019nCoV-314

Study Day	**–14 to 0[1]**	**0[1]**	**28**	**56**	**90**	**118**	**146**	**180**	**Unscheduled Visit[2, 19]**	
Window (days)[3]			**-1 to + 7**	**± 7**	**± 7**	**± 7**	**± 15**	**± 15**		
Study Visit	**Screening**	**1**	**2[19]**	**3 (Phone)**	**4[19]**	**5 (Phone)**	**6 (Phone)**	**EOS[4, 19]**	**Gen**	**Sp**
Reactogenicity/participant eDiary completion[14,15]		X								
All unsolicited AEs		X	X						X	X
MAAEs[16,17]		X	X	X	X	X	X	X	X	X
SAEs[17]	X	X	X	X	X	X	X	X	X	X
AESI (including PIMMCs, myocarditis and/or pericarditis, and complications specific to COVID-19)[17]		X	X	X	X	X	X	X	X	X
EOS form[18]								X		

Abbreviations: AE = adverse event; AESI = adverse event(s) of special interest; BMI = body mass index; ECG = electrocardiogram; eDiary = electronic participant-reported outcome diary application; ELISA = enzyme-linked immunosorbent assay; EOS = end of study; Gen = Unscheduled Visit due to a general medical issue; hACE2 = human angiotensin-converting enzyme 2; HEENT = head, eye, ear, nose, and throat (examination); ID = identification; POCBP = participants of childbearing potential; MAAE = medically attended adverse event; N = nucleocapsid (protein); NAb = neutralizing antibody; OTC = over-the-counter; PCR = polymerase chain reaction; PIMMC = potential immune-mediated medical conditions; S = spike (protein); SAE = serious adverse event; SAP = statistical analysis plan; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; Sp = Unscheduled Visit due to suspected COVID-19 symptoms.

1. The Screening visit and Day 0 visit may be combined if feasible at any given study site.
2. An Unscheduled Visit will be conducted by study personnel for safety follow-up for any participant experiencing a medical issue while on study. For general Unscheduled Visits, the investigator may also perform any of the assessments listed in the SOE if needed for the clinical evaluation of an AE. For an Unscheduled Visit due to suspected COVID-19 symptoms, confirmed symptomatic cases of COVID-19 should be recorded as an AE, SAE, or COVID-19 relevant AESI as appropriate and the visit may be conducted as a telehealth visit if required by local health regulations. Positive PCR swab results in asymptomatic participants should also be entered as an AE.
3. Should a study pause occur, visits/windows will be adjusted to allow participants to continue without protocol deviation.
4. EOS assessments will be conducted in person. Should participants decide to terminate early, a telephone call will occur to collect the maximum safety data possible.
5. Including prior and concomitant medical conditions, all COVID-19 vaccinations, all other recent vaccinations (≤ 90 days), and significant surgical procedures.
6. Specific exclusions to study vaccination will be assessed before any vaccination. Waivers for enrolling participants with exclusions will not be given.
7. Performed prior to study vaccination.

Table 1: Schedule of Events for Study 2019nCoV-314

Study Day	**–14 to 0[1]**	**0[1]**	**28**	**56**	**90**	**118**	**146**	**180**	**Unscheduled Visit[2, 19]**	
Window (days)[3]			**-1 to + 7**	**± 7**	**± 7**	**± 7**	**± 15**	**± 15**		
Study Visit	**Screening**	**1**	**2[19]**	**3 (Phone)**	**4[19]**	**5 (Phone)**	**6 (Phone)**	**EOS[4, 19]**	**Gen**	**Sp**

8. Screening only. Including age, year of birth, sex, race, ethnicity, weight, height, and BMI (derived).
9. Prior and concomitant medications, including recent and current medications at the time of screening to be reviewed to ensure eligibility criteria are fulfilled. Concomitant medications include prescription and OTC (including vaccines in the past 90 days and all COVID-19 vaccinations) taken by the participant. Do not record herbals, vitamins, and supplements.
10. Including respiratory rate, blood pressure, pulse rate, pulse oximetry and temperature (oral or via forehead/ear reader). On study vaccination days, vital sign measurements will be collected once before study vaccination to ensure participant has no evidence of fever prior to study vaccination.
11. Participants of childbearing potential only. A urine pregnancy test will be performed at Screening and prior to study vaccination. A positive urine pregnancy test at any time will result in the participant not receiving any further study vaccination. A positive urine pregnancy test at Screening will result in screen failure.
12. Full physical examination at screening to include HEENT, neck, lungs, heart, cardiovascular, abdomen and musculoskeletal system/extremities to allow for study vaccination; symptom-directed (targeted) physical examination at all other scheduled time points. Full physical examinations will be performed at any unscheduled visit.
13. Participants will be asked to report any PCR/rapid test confirmed cases of COVID-19 that occurred since last contact. For all medically attended cases of COVID-19, an attempt will be made to obtain all relevant medical records in order to assess case severity.
14. Following vaccination, participants will remain in the clinic or under study staff observation for at least 15 minutes post-vaccination to be monitored for any immediate hypersensitivity and anaphylaxis reactions.
15. Participants will utilize an eDiary to record reactogenicity following vaccination and for an additional 6 days after vaccination. All eDiary entries will be reviewed and assessed by the investigator.
16. All MAAEs will be collected for 28 days following vaccination. Only treatment related MAAEs will be collected throughout the duration of the study.
17. Details regarding the dates and nature of any health encounters associated with SAEs, AESIs, and/or MAAEs that required a visit with a healthcare provider will be collected in the eCRF.
18. EOS form will be completed for all participants, including participants who are terminated early.
19. These visits may take place at the homes of trial participants or another safe, alternative location by a professionally trained Home Health Care provider.

2 INTRODUCTION

2.1 Background

Coronaviruses are medium sized, enveloped, positive-stranded ribonucleic acid (RNA) viruses, with a characteristic crown-like appearance in electron micrographs due to circumferential studding of the viral envelope with projections comprising the spike (S) protein. There are 4 different strains (229E, OC43, NL63, and HKU1), which are ubiquitous in humans and generally result in mild upper respiratory illnesses and other common cold symptoms, including malaise, headache, nasal discharge, sore throat, fever, and cough (Su 2016). In addition, other coronavirus strains are widespread in animals, where they typically cause enteric disease. These zoonotic coronaviruses have been known to evolve into strains that can infect humans with serious consequences, including severe acute respiratory syndrome coronavirus (SARS-CoV) from 2002 to 2003, Middle East Respiratory Syndrome (MERS)-CoV since 2012, and most recently, the novel SARS-CoV-2 since 2019 (Habibzadeh 2020).

In late December of 2019, an outbreak of respiratory disease caused by a novel coronavirus (2019nCoV) was detected in Wuhan, Hubei province, China. The virus' rapidly discerned genetic relationship with the 2002-2003 SARS-CoV has resulted in adoption of the name "SARS-CoV-2," with the disease being referred to as Coronavirus disease 2019 (COVID-19).

Thereafter, reports from the United Kingdom (UK), Brazil, India, and South Africa revealed the emergence of the B.1.1.7 (Alpha), P.1 (Gamma), B.1.617.2 (Delta), and B.1.351 (Beta) and B.1.1.529 (Omicron) variants of SARS-CoV-2, respectively, with confirmed acquisition of mutations in key antigenic sites in the receptor-binding domain and N-terminal domain of the spike (S) protein. Omicron subvariants have persisted in circulation, with the XBB.1.5 subvariant accounting for approximately 82% of circulation as of 28 Apr 2023 (CDC 2022, CDC 2023). Current evidence demonstrates that variant strain mutations such as those in the Omicron XBB.1.5 sublineage confer the ability to evade both natural and vaccine induced neutralizing antibodies (Qu 2023, Yue 2023, Zhang 2022).

Initial actions to stay ahead of SARS-CoV-2 evolution included direction from the US Food and Drug Administration (FDA) to recommend the development vaccines containing an Omicron BA.4/5 component (Marks 2022). On 26 January 2023, the Vaccines and Related Biological Products Advisory Committee (VRBPAC) met to discuss further updates to the composition of COVID-19 vaccines. At the conclusion of this meeting, the VRBPAC voted to harmonize the vaccine strain composition of primary series and booster vaccinations into a single, updated composition for the fall 2023 vaccination campaign.

The present study will assess the safety and immunogenicity of an Omicron XBB.1.5 subvariant vaccine (NVX-CoV2601) alone as a monovalent product or in combination with the prototype Novavax vaccine (NVX-CoV2373) as a bivalent product in an adolescent population. The study will enroll adolescent participants ≥ 12 to < 18 years of age who have previously received

≥ 2 doses of the Moderna and/or Pfizer-BioNTech monovalent and/or bivalent vaccines
≥ 90 days prior to study vaccination.

2.1.1 Description of SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccines

NVX-CoV2373 is the prototype SARS-CoV-2 rS nanoparticle vaccine construct adjuvanted with Matrix-M adjuvant that is intended to be used for the active immunization for the prevention of mild, moderate, and severe COVID-19 caused by SARS-CoV-2. NVX-CoV2373 is constructed from the full-length, wild-type SARS-CoV-2 S glycoprotein (GP) based on the GenBank gene sequence MN908947, nucleotides 21563-25384 from the 2019 SARS-CoV-2 genome (Wuhan-Hu-1 strain). In the wake of emerging SARS-CoV-2 variants, Novavax continues to produce and investigate rS nanoparticle vaccines using the sequenced genomes from several variant strains (multiple potential sequences being evaluated with one to be down-selected for final production). The S protein from each virus is a type 1 trimeric GP that is produced as an inactive S0 precursor. The S-gene is then codon-optimized for expression in *Spodoptera frugiperda* (Sf9) insect cells.

All SARS-CoV-2 rS vaccines are adjuvanted with Matrix-M adjuvant. Adjuvants are compounds which, when combined with a specific vaccine antigen, serve to increase the immune response to the vaccine. In general, adjuvants work by engaging one or more components of the innate immune system. Matrix-M is a saponin-based adjuvant, derived from the bark of the *Quillaja saponaria* Molina tree, which can be co-administered with an antigen to induce a targeted and enhanced immune response. The proposed mode of action of Matrix-M adjuvant does not include a depot effect, but rather occurs through a combination of activities, including recruitment and activation of innate immune cells to the site of vaccine injection, 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 investigational products used in this study are manufactured by Serum Institute of India (SII) through a partnership with Novavax. Production of NVX-CoV2601 was initiated based on master virus seeds produced and supplied to SII by Novavax. Aside from the differences in antigenic composition compared to NVX-CoV2373; the manufacturing process and final composition will be the same as for the authorized NVX-CoV2373 vaccine.

Additional product information, including manufacturing details and supportive clinical and nonclinical study summaries, can be found in the SARS-CoV-2 rS Investigator's Brochure (IB) (Novavax 2022).

2.1.2 Supportive Nonclinical Data

Supportive nonclinical data are available through studies conducted for the Novavax manufactured prototype SARS-CoV-2 rS product (NVX-CoV2373). Pharmacological properties of the vaccines used in this study are expected to be equivalent to those produced by Novavax.

Nonclinical safety, immunogenicity, and protective efficacy have now been confirmed in Phase 3 clinical trials. Nonclinical data can be found in the Investigator's Brochure.

A good laboratory practice (GLP)-compliant developmental and reproductive toxicity study was completed in Sprague-Dawley rats. Females were immunized with placebo, 5 µg of SARS-CoV-2 rS antigen with 10 µg of Matrix-M adjuvant, or 10 µg of Matrix-M adjuvant alone. These doses were approximately 40-fold in excess of the human dose, on a weight-adjusted basis, in a 50 kg human female. Doses were given on pre-mating Days 1 and 15, and then, after mating, at gestational Days 7 and 15. Dams immunized with antigen plus adjuvant, but not adjuvant alone, had strong anti-S immunoglobulin G (IgG) responses, and vaccine-induced antibody was transferred transplacentally to the fetuses. Mating and fertility, as well as the number and viability of fetuses, were unaffected by adjuvant or complete vaccine. There was no treatment effect on fetal malformations or skeletal abnormalities. In dams allowed to deliver, receipt of adjuvant or complete vaccine did not affect the gestational duration at delivery or the number of live pups; and there was also no impact of the attainment of developmental milestones by pups through 21 days of life.

2.1.3 Supportive Clinical Data

Supportive clinical data are available via studies conducted using Novavax manufactured SARS-CoV-2 rS products.

As of this date, clinical data are available from studies performed using NVX-CoV2373 and an Omicron BA.1 variant vaccine (NVX-CoV2515).

The clinical development program for Novavax's SARS-CoV-2 rS with Matrix-M adjuvant primarily comprises 4 clinical studies: a Phase 1-2 study of SARS-CoV-2 rS with or without Matrix-M adjuvant in healthy adult participants 18 to 59 years of age (Study 2019nCoV-101–Part 1) and SARS-CoV-2 rS with Matrix-M adjuvant in healthy adult participants 18 to 84 years of age (Study 2019nCoV-101 – Part 2); a Phase 2a/b study of SARS-CoV-2 rS with Matrix-M adjuvant in healthy adult participants 18 to 84 years of age living without human immunodeficiency virus (HIV) and medically stable adult participants 18 to 64 years of age living with HIV (Study 2019nCoV-501); and 2 Phase 3 studies in healthy and medically stable adult participants ≥ 18 years of age and adolescent participants 12 to < 18 years of age (Study 2019nCoV-301) and 18 to 84 years of age (Study 2019nCoV-302).

2.1.3.1 Clinical Pharmacology and Safety

Clinical data from Phase 1-2 trials and additional clinical data from Phase 3 trials can be found in the Investigator's Brochure and their respective publications (Novavax 2022, Keech 2020, Mallory 2022, Dunkle 2021, Heath 2021, Shinde 2021). In total, over 30,000 participants have been immunized with NVX-CoV2373 in clinical trials and 2,266,287 NVX-CoV2373 doses have been administered in Australia, Canada, European Union (EU), Israel, Japan, New Zealand,

Singapore, South Korea, Switzerland, Taiwan, and the United States (US) cumulatively as of 17 November 2022.

Study 2019nCoV-302 was a Phase 3, randomized (1:1), observer-blinded, placebo-controlled trial evaluating the efficacy, safety, and immunogenicity of 5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant, administered 21 days apart on Days 0 and 21 as a coformulation, in 15,139 healthy and medically stable (with comorbidities) participants 18 to 84 years of age conducted in the United Kingdom (UK). After the initial vaccination period, participants remained blinded and crossed over to the opposite treatment arm. An analysis of the primary efficacy endpoint, which included both immunogenicity and safety data, was performed. A total of 106 cases of polymerase chain reaction (PCR) -confirmed symptomatic mild, moderate, or severe COVID-19 were accrued for the final prespecified analysis of the primary endpoint, with 10 (0.1%) in the NVX-CoV2373 group and 96 (1.4%) in the placebo group. All but 5 cases were mild or moderate in severity, with all 5 severe cases occurring in the placebo group. The resultant vaccine efficacy of NVX-CoV2373 to prevent symptomatic mild, moderate, or severe COVID-19 in baseline seronegative (to SARS-CoV-2) adult participants was 89.7% (95% CI: 80.2, 94.6; $p < 0.001$), with a lower bound confidence interval (LBCI) > 30% meeting the prespecified study success criterion. PCR results of the final analysis by SARS-CoV-2 strain showed vaccine efficacy of 86.3% (95% CI: 71.3, 93.5) for the B.1.1.7 (Alpha) variant and 96.4% (95% CI: 73.8, 99.5) for the ancestral (Wuhan) strain. NVX-CoV2373 induced robust immune responses (anti-S IgG and neutralizing antibody [Nab]), which were 1.3-fold (anti-S IgG) and 1.4-fold (Nab) higher in the younger age cohort (18 to 64 years) than in the older age cohort (65 to 84 years), but seroconversion rates (SCRs) were at least 98% in both age cohorts. NVX-CoV2373 was well tolerated, with similar frequencies of serious adverse events (SAEs), medically attended adverse events (MAAEs), and adverse events of special interest (AESIs) compared to placebo. Solicited local and systemic reactogenicity in a subset of 2,714 participants were higher for NVX-CoV2373 than placebo, but the majority of reported events were classified as grade 1 following first vaccination and grade 1 or grade 2 following second vaccination. The most frequent local AEs following each vaccination were tenderness and pain, with relatively short median durations following first (≤ 2.0 days) and second (≤ 3.0 days) vaccination. The most frequent solicited systemic AEs following each vaccination were headache, fatigue, and muscle pain, with relatively short median durations following first (≤ 1.5 days) and second (≤ 2.0 days) vaccination. Across the 2 age strata, participants in the older age cohort (65 to 84 years of age) reported a lower frequency and intensity of solicited local and systemic treatment emergent adverse events (TEAEs) than participants in the younger age cohort (18 to 64 years of age).

Study 2019nCoV-301 is a Phase 3, randomized (2:1), observer-blinded, placebo-controlled trial with a pediatric expansion evaluating the efficacy, safety, and immunogenicity of NVX-CoV2373, administered 21 days apart on Days 0 and 21 as a coformulation, in 29,582 healthy and medically stable (with comorbidities or at high risk for COVID-19) adult participants 18 years of age and older conducted in the United States (US) and Mexico and the safety and immunogenicity of NVX-CoV2373 in 2,247 healthy adolescent participants 12 to < 18 years of

age conducted in the US. In adults, final analysis of the primary efficacy endpoint yielded a VE of 90.41% (95% CI: 83.81, 94.32) for all participants. In addition, NVX-CoV2373 induced robust immune responses and safety data reflected an acceptable safety profile. These data were submitted to the FDA in support of a request for Emergency Use Authorization. Subsequently, safety and immunogenicity data following a booster dose of NVX-CoV2373 from this study supported Emergency Use Authorization of the vaccine as a booster dose.

The pediatric expansion of Study 2019nCoV-301 evaluated the efficacy, safety, and immunogenicity of NVX-CoV2373 in participants 12 to < 18 years of age. Out of the 1468 and 730 participants in the NVX-CoV2373 and placebo groups, respectively, who received both vaccinations, 1277 (87.0%) and 618 (84.7%), respectively, had at least 60 days of follow-up after their second vaccination. NVX-CoV2373 was well tolerated and elicited significantly enhanced - immune responses, with similar frequencies of SAEs, MAAEs, and AESIs compared to placebo. As of the data cut-off date for the primary efficacy analysis among 1,197 participants receiving 2 doses of NVX-CoV2373 and 590 participants receiving 2 doses of placebo, a two-dose regimen of NVX-CoV2373 administered at least 21 days apart demonstrated high efficacy for preventing PCR-confirmed symptomatic mild, moderate, or severe COVID-19 (VE = 79.56% [95% CI: 46.87,92.13]). Of note, efficacy data were collected during the time in which the Delta variant of concern (VOC) was the predominant circulating variant in the US.

As a continuation of the pediatric expansion of Study 2019nCoV-301, a third (booster) dose of NVX-CoV2373 was administered in an open-label manner to participants who remained in study follow-up (either blinded or unblinded) and had received their full primary series of NVX-CoV2373 as planned. Booster doses were administered no less than 5 months after completion of active vaccination. Immunogenicity and safety data following the booster dose demonstrated non-inferiority of the booster dose of NVX-CoV2373 vs the primary series, with a GMFR of 2.7 (95% CI: 2.0, 3.5) and an LB of the 95% CI > 1.0 (primary endpoint, NAb titers vs the ancestral strain), and found the dose was well tolerated with an acceptable safety profile comparable with the primary series and similar data in adults.

Study 2019nCoV-311 is an ongoing Phase 3, multi-part, randomized, observer-blinded trial in healthy adult participants who previously received prototype mRNA COVID-19 vaccines, with their last dose of mRNA vaccine approximately 6 months prior to study vaccination. In Part 1 of the study, 831 participants were randomized 1:1:1 to receive a single booster dose of either NVX-CoV2515, NVX-CoV2373, or a bivalent vaccine (NVX-CoV2515 + NVX-CoV2373, 5 µg total antigen). An interim analysis performed 28 days after study vaccination found the primary objective of the study was met, achieving the endpoints needed to demonstrate that the Omicron 5 specific vaccine (NVX-CoV2515) produced a superior antibody response to the Omicron BA.1 subvariant when compared to the prototype vaccine (NVX-CoV2373) at Day 14. Safety analyses determined NVX-CoV2515, NVX-CoV2373, and the bivalent vaccine were all well-tolerated with comparable and acceptable safety profiles.

2.1.4 Benefit: Risk Assessment

The SARS-CoV-2 rS nanoparticle vaccines contain purified protein antigens. They cannot replicate, the protein is not produced using infectious SARS-CoV-2, nor can the vaccines cause COVID-19. However, in common with all vaccines produced in cell culture or other systems, the SARS-CoV-2 rS nanoparticle vaccines contain residual non-vaccine proteins derived from the production system, and sensitization to these, or the SARS-CoV-2 S protein itself, may theoretically occur. While the occurrence of anaphylaxis is possible with the administration of any vaccine, whether licensed or in development, no such reactions have been observed in any of the Sponsor's clinical trials to date. As clinical data become available, with increased exposure it is possible that this profile may change. The risk of AEs related to hypersensitivity will be mitigated by observation of participants for at least 15 minutes after study vaccination.

The risk for enhanced COVID-19 in immunized participants is a theoretical risk. There is currently no evidence for immunoenhancement in nonclinical testing of SARS-CoV-2 rS or other Novavax baculovirus-Sf9-based vaccines taken into nonclinical evaluation or clinical trials.

No risks have been identified in nonclinical or early clinical testing of SARS-CoV-2 or other coronavirus vaccines (SARS-CoV and MERS-CoV) developed using the baculovirus-Sf9 system to date. In supportive toxicology studies with other viral GP nanoparticle vaccines developed using the baculovirus-Sf9 system with different antigens, findings were generally consistent with an immune response to the vaccine formulations. These toxicological investigations indicated that baculovirus-Sf9-produced antigens (up to 240 µg total nanoparticle dose) with Matrix-M adjuvant (up to 100 µg) were well tolerated in the animal and antigen system tested with no evidence of toxicity suggestive of any unusual risk or target organ for toxicity. Non-adverse findings, including local injection site inflammation and serum chemical markers of inflammation (such as C-reactive protein), were transient and considered consistent with immune system stimulation consequent to immunization.

Myocarditis or pericarditis has been reported following vaccination with NVX-CoV2373 in clinical trials and following emergency use authorization, and it is possible that these reports represent vaccine-associated AEs similar to those associated with messenger ribonucleic acid (mRNA) COVID-19 vaccines. While available data may not be sufficient to definitively establish a causal relationship with NVX-CoV2373, neither can a causal relationship be excluded.

Myocarditis or pericarditis associated with mRNA vaccines has been reported in greatest numbers in males under the age of 30 years following a second dose, but cases have been reported in older males and in females as well, and also following the first dose. While some cases required intensive care support, available data from short-term follow-up suggest that most individuals have had resolution of symptoms with conservative management. Information is not yet available about potential long-term-sequelae.

The Centers for Disease Control and Prevention (CDC) has published clinical considerations for myocarditis and pericarditis after receipt of mRNA COVID-19 vaccines among adolescents and young adults which makes specific recommendations for the management of myocarditis and pericarditis (CDC 2021). A surveillance and management plan for suspected myocarditis and/or pericarditis cases based on CDC and American Heart Association (AHA) recommendations has been implemented in the clinical development plan of NVX-CoV2373 (CDC 2021, Law 2021, Gargano 2021).

Findings to date suggest that SARS-CoV-2 rS when administered with Matrix-M adjuvant (NVX-CoV2373) demonstrated an acceptable safety profile and robust immunogenicity profile in healthy and medically stable adult participants 18 to 84 years. Results of an interim 35-day reactogenicity analysis on 1,283 participants aged 18 to 84 years in Part 2 of Study 2019nCoV-101 and 2,714 participants 18 to 84 years in Study 2019nCoV-302 showed a similar reactogenicity profile between younger and older participants, with both local and systemic reactogenicity events occurring less frequently in older adults. In addition, nearly 31,000 individuals have to date received at least 1 dose of NVX-CoV2373 and ongoing reviews of the accumulated safety data support continued development of the vaccine and vaccines based on the same platform.

For the NVX-CoV2373 vaccine, clinical efficacy results are also available from studies run in the UK and South Africa. In the UK study (Study 2019nCoV-302), the overall efficacy of the vaccine was 89.7% (95% CI: 80.2, 94.6) and, in post hoc analyses, efficacy estimates for the B.1.1.7 (Alpha) variant and for the ancestral strain were 86.3% and 96.4%, respectively. In the South Africa study (Study 2019nCoV-501), the efficacy of the vaccine in all study participants was 48.6% (95% CI: 28.4, 63.1) and 55.4% (95% CI: 35.9, 68.9) in participants who were HIV-negative. The efficacy estimates in South Africa were generated in a period of > 90% B.1.351 (Beta) variant virus circulation.

2.2 Study Rationale

In response to the emergence of the Omicron variant of SARS-CoV-2, Novavax, in conjunction with SII, has developed a Matrix-M-adjuvanted rS protein nanoparticle vaccine using the sequenced genome from the Omicron XBB.1.5 subvariant (NVX-CoV2601) for the prevention of disease caused by SARS-CoV-2 using the same recombinant baculovirus and insect cell vaccine platform technology employed previously to produce other SARS-CoV-2, influenza, and respiratory syncytial virus vaccines. NVX-CoV2601 will also be used in combination with NVX-CoV2373 in the form of a site-mixed bivalent vaccine (NVX-CoV2373 + NVX-CoV2601) to explore the safety and immunogenicity of vaccines containing antigen for both the ancestral (Wuhan) and Omicron subvariant strain of SARS-CoV-2.

In sera tested from vaccinees who had received prior mRNA vaccines, Omicron neutralization was completely lost in > 50% of individuals accompanied by a 43-fold geometric mean titer (GMT) decrease for the Moderna vaccine and 122-fold decrease for the Pfizer-BioNTech vaccine. In subjects who had been recently boosted, Omicron neutralization for the Moderna

vaccine was only 6-fold lower than for the original wild-type neutralization, similarly for the Pfizer-BioNTech vaccine, the fold decrease was only 4 (Garcia-Beltran 2021). These tests show that 2-doses of mRNA vaccines are effective against the wild-type variant, but suboptimal for inducing equivalent neutralizing antibodies to the Omicron variant. In participants who had been boosted with an mRNA vaccine within the last 3-months showed correlation in cross-neutralization between the wild-type variant and the Omicron variant.

Novavax, Inc. is developing recombinant vaccines adjuvanted with the saponin based Matrix-M adjuvant for the prevention of disease caused by SARS-CoV-2. Both nonclinical and clinical data to date support continued clinical development of SARS-CoV-2 rS vaccines combined with Matrix-M adjuvant as potential vaccines against SARS-CoV-2.

This study is designed to assess the safety and immunogenicity of the Novavax Omicron XBB.1.5 subvariant vaccine (NVX-CoV2601) alone as a monovalent product 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.

If favorable immunogenicity and safety profiles are observed following the booster doses of the bivalent product (NVX-CoV2373 + NVX-CoV2601), this would support the use of variant and/or bivalent vaccines in the global COVID-19 vaccination effort.

3 OBJECTIVES AND ENDPOINTS

The primary objectives in this study are to assess the overall safety of 1 heterologous booster dose of NVX-CoV2601 and the bivalent vaccine (NVX-CoV2373 + NVX-CoV2601) and to describe the NAb responses induced against the Omicron XBB.1.5 strain. An overview of the study objectives and endpoints is provided in Table 2.

Table 2: Study 2019nCoV-314 Objectives and Endpoints

Tier	Objectives	Endpoints
Primary Safety Objective and Endpoints	To assess the overall safety of 1 heterologous booster dose of NVX-CoV2601 and the bivalent vaccine (NVX-CoV2373 + NVX-CoV2601).	• Incidence, duration, and severity of solicited local and systemic AEs for 7 days following vaccination. • Incidence, severity, and relationship of unsolicited AEs through 28 days after vaccination • Incidence and severity of MAAEs attributed to study vaccine, AESIs (predefined list including PIMMCs, myocarditis and/or pericarditis, and complications specific to COVID-19), and SAEs through day 180 or EOS.

Table 2: Study 2019nCoV-314 Objectives and Endpoints

Tier	Objectives	Endpoints
Primary Immunogenicity Objective and Endpoints	To describe the NAb response induced by NVX-CoV2601 and the bivalent vaccine (NVX-CoV2373 + NVX-CoV2601) against the Omicron XBB.1.5 strain.	• NAb GMTs to the Omicron XBB.1.5 strain, assessed at Day 28 following initial study vaccination. • NAb geometric mean fold rise (GMFR) at Day 28 from baseline (Day 0).
Secondary Objectives	To describe the NAb response induced by NVX-CoV2601 and the bivalent vaccine (NVX-CoV2373 + NVX-CoV2601) against the Omicron XBB.1.5 strain over time.	• NAb GMTs to the Omicron XBB.1.5 strain at relevant time points (Days 0, 90, and 180). • NAb GMFR at relevant time points (Days 90 and 180) from baseline (Day 0)
	To describe immunoglobulin G (IgG) antibody levels induced by NVX-CoV2601 and the bivalent vaccine (NVX-CoV2373 + NVX-CoV2601) against the Omicron XBB.1.5 strain over time.	• IgG GMEUs to the Omicron XBB.1.5 S protein at relevant time points (Days 0, 90, and 180). Derived/calculated endpoints based on these data will include GMFR.
Exploratory	To describe the NAb and IgG antibody responses induced by NVX-CoV2601 and the bivalent vaccine (NVX-CoV2373 + NVX-CoV2601) against the ancestral (Wuhan) strain over time.	• NAb titers and IgG GMEUs to the ancestral (Wuhan) strain at relevant time points (Days 0, 90, and 180). Derived/calculated endpoints based on these data will include GMFR.
	To describe antibody responses in a human angiotensin converting enzyme-2 (hACE2) receptor binding inhibition assay induced by NVX-CoV2601 and the bivalent vaccine (NVX-CoV2373 + NVX-CoV2601) to the Omicron XBB.1.5 and ancestral (Wuhan) strains over time.	• GMTs to the Omicron XBB.1.5 and ancestral (Wuhan) strains at relevant time points (Days 0, 90, and 180). Derived/calculated endpoints based on these data will include GMFR.
	To describe antibody responses in a mucosal IgA-mediated hACE2 receptor binding inhibition assay induced by NVX-CoV2601 and the bivalent vaccine (NVX-CoV2373 + NVX-CoV2601) to the Omicron XBB.1.5 and ancestral (Wuhan) strains over time.	• GMTs to the Omicron XBB.1.5 and ancestral (Wuhan) strains at relevant time points (Days 0 and 28). Derived/calculated endpoints based on these data will include GMFR.
	To utilize additional assays (current or to be developed) to better characterize the immune response for future vaccine development needs.	• Additional endpoints to evaluate immune responses may be developed based on the assays used.
	To characterize the severity of COVID-19 in participants who become infected during the course of the study.	• Detected case will be characterized as mild, moderate, or severe as assessed using the provided criteria.

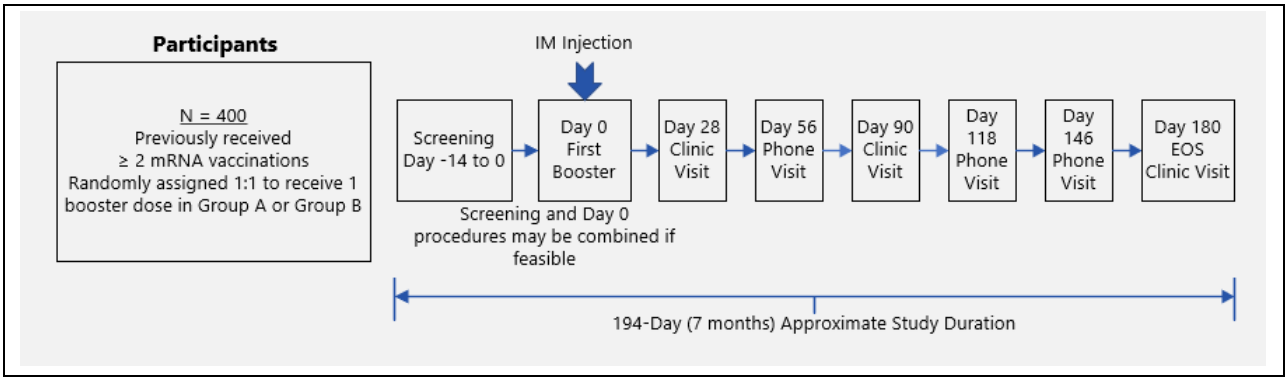
Abbreviations: AE = adverse event; AESI = adverse event(s) of special interest; ELISA = enzyme-linked immunosorbent assay; GMEU = geometric mean ELISA units; GMFR = geometric mean fold rise; GMT = geometric mean titer; hACE2 = human angiotensin-converting enzyme 2; IgG = immunoglobulin G; NAb =

neutralizing antibody; MAAE = medically attended adverse event; NAb = neutralizing antibody; PIMMC = potentially immune-mediated medical condition; S = spike; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

4 STUDY PLAN

4.1.1 Study Schematic

Figure 1: Flow Diagram for Study 2019nCoV-314



Abbreviations: EOS = end of study; IM = intramuscular.
Note: Group A = NVX-CoV2601 Day 0; Group B = Bivalent NVX-CoV2373 + NVX-CoV2601 Day 0.

4.1.2 Study Design

This is a Phase 3, randomized, observer blinded study to evaluate the safety and immunogenicity of a booster dose of Omicron XBB.1.5 subvariant SARS-CoV-2 rS vaccines adjuvanted with Matrix-M adjuvant in previously vaccinated participants.

Approximately 400 adolescents who have received a regimen of ≥ 2 doses of the Moderna and/or Pfizer-BioNTech monovalent and/or bivalent COVID-19 vaccines ≥ 90 days previously will be enrolled and randomized 1:1 to Group A or Group B.

- Group A: 1 dose of NVX-CoV2601 (1 on Day 0)
- Group B: 1 dose of bivalent NVX-CoV2373 + NVX-CoV2601 (1 on Day 0)

Participants will remain on study for immunogenicity and safety data collection through Day 180. A tabular summary of the study design is provided below in Table 3, and a complete outline of study procedures is provided in Section 6.1.2.

Table 3: Study Groups and Treatments

Group	Previous Vaccine	Novavax Vaccine Booster (antigen/adjuvant)	n
A	≥ 2 doses Moderna and/or Pfizer-BioNTech	NVX-CoV2601 (5 µg/50 µg)	200
B		Bivalent NVX-CoV2373 + NVX-CoV2601 (5 µg/50 µg [total])	200

4.1.3 Design Rationale

This study is designed to assess the safety and immunogenicity of the Novavax Omicron XBB.1.5 subvariant vaccine (NVX-CoV2601) alone as a monovalent product 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.

Enrolled participants are intended to match a representative US adolescent population, including participants with common vaccination histories and with no restrictions on prior COVID-19 exposure. The sample size and study duration were selected to prioritize the collection of safety data.

If favorable immunogenicity and safety profiles are observed following the booster doses of the bivalent product (NVX-CoV2373 + NVX-CoV2601), this would support the use of variant and/or bivalent vaccines in the global COVID-19 vaccination effort.

5 POPULATION

5.1 Recruitment

Approximately 400 participants will be enrolled. Participants will be screened across approximately 25 different study sites located in the US and Canada (Canadian sites contingent upon additional approval).

Participants will be medically stable male and nonpregnant females ≥ 12 to < 18 years of age who have previously received ≥ 2 doses of the Moderna and/or Pfizer-BioNTech monovalent and/or bivalent vaccines ≥ 90 days prior to study vaccination.

5.1.1 Definitions

Participants officially enter the Screening Period following provision of informed consent.

A screen failure is a consented participant who has been deemed ineligible on the basis of 1 or more eligibility criteria or who has withdrawn consent prior to treatment assignment.

An enrolled participant is one who has been deemed eligible and has been assigned to a treatment group.

5.1.2 Inclusion Criteria

To be included in this study, each individual must satisfy all of the following criteria:

1. Adolescents ≥ 12 to < 18 years of age at screening
2. Participant and parent(s)/caregiver(s) or legally acceptable representative willing and able to give informed consent and assent, as required, prior to study enrollment and to comply with study procedures.
3. Participants of childbearing potential (defined as any participant who has experienced menarche and who is NOT surgically sterile [ie, hysterectomy, bilateral tubal ligation, or bilateral oophorectomy] or postmenopausal [defined as amenorrhea ≥ 12 consecutive months]) must agree to be heterosexually inactive from at least 28 days prior to enrollment and through the end of the study OR agree to consistently use a medically acceptable method of contraception listed below from ≥ 28 days prior to enrollment and through the end of the study.
    a. Condoms (male or female) with spermicide (if acceptable in country)
    b. Diaphragm with spermicide
    c. Cervical cap with spermicide
    d. Intrauterine device
    e. Oral or patch contraceptives
    f. Norplant®, Depo-Provera®, or other in country regulatory approved contraceptive method that is designed to protect against pregnancy
    g. Abstinence, as a form of contraception, is acceptable if in line with the participant's lifestyle

    NOTE: Periodic abstinence (eg, calendar, ovulation, sympto-thermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
4. Is medically stable, as determined by the investigator (based on review of health status, vital signs [to include body temperature], medical history, and targeted physical examination [to include body weight]). Vital signs must be within medically acceptable ranges prior to the vaccination.
5. Agrees to not participate in any other SARS-CoV-2 prevention or treatment trials for the duration of the study.

    NOTE: For participants who become hospitalized with COVID-19, participation in investigational treatment studies is permitted.

6. Have previously received ≥ 2 doses of the Moderna and/or Pfizer-BioNTech monovalent and/or bivalent COVID-19 vaccines with the last dose having been given ≥ 90 days previously prior to study vaccination.

5.1.3 Exclusion Criteria

If an individual meets any of the following criteria, he or she is ineligible for this study:

1. Received COVID-19 vaccines other than Moderna and/or Pfizer-BioNTech in the past, inclusive of clinical trial COVID-19 vaccines.
2. Participation in research involving receipt of investigational products (drug/biologic/device) within 90 days prior to study vaccination.
3. Received influenza vaccination within 14 days prior to study vaccination.
4. Received any vaccine ≤ 45 days prior to study vaccination, except for rabies, human papilloma virus (HPV), tetanus-diphtheria (Td), tetanus, diphtheria, and pertussis (TDaP/DTap), hepatitis B virus (HBV), and meningococcal vaccines which may be given as medically indicated.
5. Any known allergies to products contained in the investigational product.
6. Any history of anaphylaxis to any prior vaccine.
7. Autoimmune or immunodeficiency disease/condition (iatrogenic or congenital) requiring ongoing immunomodulatory therapy.

   NOTE: Stable endocrine disorders (eg, thyroiditis, pancreatitis), including stable diabetes mellitus with no history of diabetic ketoacidosis) are NOT excluded.

8. Chronic administration (defined as > 14 continuous days) of immunosuppressant, systemic glucocorticoids, or other immune-modifying drugs within 90 days prior to study vaccination.

   NOTE: An immunosuppressant dose of glucocorticoid is defined as a systemic dose ≥ 10 mg of prednisone per day or equivalent. The use of topical or intranasal glucocorticoids is permitted. Topical tacrolimus and ocular cyclosporin are permitted.

9. Received immunoglobulin, blood-derived products, or immunosuppressant drugs within 90 days prior to study vaccination, except for rabies immunoglobulin which may be given if medically indicated.
10. Active cancer (malignancy) on therapy within 3 years prior to study vaccination (with the exception of adequately treated non-melanomatous skin carcinoma or lentigo maligna and uterine cervical carcinoma in situ without evidence of disease, at the discretion of the investigator).
11. Participants who are breastfeeding, pregnant, or who plan to become pregnant prior to the end of study.

12. Suspected or known history of alcohol abuse or drug addiction within 2 years prior to the study vaccine dose that, in the opinion of the investigator, might interfere with protocol compliance.
13. Any other condition that, in the opinion of the investigator, would pose a health risk to the participant if enrolled or could interfere with evaluation of the study vaccine or interpretation of study results (including neurologic or psychiatric conditions likely to impair the quality of safety reporting).
14. Study team member or immediate family member of any study team member (inclusive of Sponsor, clinical research organization [CRO], and study site personnel involved in the conduct or planning of the study).
15. Participants with a history of myocarditis or pericarditis.
16. Respiratory symptoms in the past 3 days (ie, cough, sore throat, difficulty breathing).
17. Temperature of > 38°C within 24 hours of planned study vaccination (site measured or participant measured).
18. Blood pressure of ≥ 160/100 mmHg.

5.2 Other Considerations for Eligibility Criteria

Participants meeting any of the following criteria may have planned study vaccination deferred for a later date, but these criteria are not exclusionary for study enrolment.

- Respiratory symptoms in the past 3 days (ie, cough, sore throat, difficulty breathing). Participant may be vaccinated once all symptoms have been resolved for > 3 days. Out-of-window study vaccination is allowed for this reason (see NOTE).
- Temperature of > 38°C within 24 hours of planned study vaccination (site measured or participant measured). Participant may be vaccinated once the fever has resolved and there has not been any temperature measured as being > 38°C for > 3 days without anti-pyrectics. Out-of-window study vaccination is allowed for this reason (see NOTE).

  NOTE: PCR testing for SARS-CoV-2 is likely to be indicated for either of the above reasons or if COVID-19 is suspected based on other symptoms or for potential exposure to SARS-CoV-2 infection through close contacts or based on local epidemiology.

- Any participant who is otherwise eligible with a blood pressure of ≥ 160/100 mmHg may be retested onsite several times over a 3-hour interval to achieve a lower blood pressure. If the blood pressure remains ≥ 160/100 mmHg, study vaccination should be deferred for a later date if, at that time, the participant's baseline blood pressure is found to be < 160/100 mmHg.

- Participants found to be SARS-CoV-2 positive during the study may be excluded from some analyses as per the statistical analysis plan (SAP) but will not be excluded from participation in the study.

6 STUDY CONDUCT

A complete description of study procedures for participants is provided in Section 6.1.2 and a SOE is provided in Table 1.

6.1 Study Summary

6.1.1 Scheduled Study Visits

All participants will follow the same treatment and assessment schedule and will remain on study for immunogenicity and safety data collection through Day 180, for a total study duration of up to 194 days (approximately 7 months).

During the study, participants will have the option of remote (home) visits for Visits 2 (Day 28), 4 (Day 90), Unscheduled (UNSCH) and EOS (Day 180). These home visits will be conducted by Illingworth Research Group who will act as an extension of the study trial sites. Illingworth Staff will be trained in the study and oversight will be provided by the PI they are assigned to support. Tasks conducted by the Illingworth Research team will include but not be limited to mobile research nursing, patient concierge, medical photography (if applicable) and any clinical research services/assessments as documented in the study protocol Schedule of Events and study plans for each visit conducted.

6.1.1.1 Scheduled Study Visits

Scheduled study visits will occur for Screening and at Days 0, 28, 56, 90 118, 146, and 180:

- Screening Period (Days -14 to 0).
- Day 0: Randomization and booster administration.
  - Screening and Day 0 procedures can be conducted on the same day when feasible.
- Day 28: Safety and immunogenicity follow-up for all participants.
- Day 56: Phone Visit - Safety follow-up for all participants.
- Day 90: Safety and immunogenicity follow-up for all participants.
- Day 118: Phone Visit - Safety follow-up for all participants.
- Day 146: Phone Visit - Safety follow-up for all participants.
- Day 180: EOS visit for all participants. EOS procedures will be conducted via site visit when possible. These procedures should also be conducted for all participants upon early termination.

On vaccination Day 0, participants will remain in the clinic or under study staff observation for at least 15 minutes post-vaccination to be monitored for any immediate hypersensitivity and anaphylaxis reactions. Participants will utilize an electronic diary (eDiary) to record reactogenicity following vaccination. All participants will be asked to record reactogenicity on the day of vaccination and for an additional 6 days after vaccination. Should any reactogenicity event extend beyond 6 days after vaccination (toxicity grade ≥ 1), then it will be recorded using the Continuing Solicited AE form and followed to resolution per ICH guidelines for dataset capture. The toxicology grading scale implemented in the eDiary for the study is included in Appendix 2.

Qualitative PCR tests will be performed on all participants on study Day 0. Confirmed symptomatic cases of COVID-19 should be recorded as an AE, SAE, or COVID-19 relevant AESI as appropriate. Positive PCR swab results in asymptomatic participants should also be entered as an AE.

6.1.1.2 Unscheduled Study Visits

Unscheduled Visits may be conducted throughout the duration of the study either via in-person or by a Home Health Care provider as deemed necessary by the principal investigator. In many cases, they may be conducted by study personnel for safety follow-up for any participant experiencing a medical issue while on study. During an Unscheduled Visit, the principal investigator may elect to perform any of the assessments listed in the SOE (Table 1) including blood sample collection, physical assessments, or other optional testing for clinical evaluation of an AE. In situations where the unscheduled visit is not due to respiratory/non-respiratory symptoms consistent with suspected COVID-19, the visit may be done as an in-person clinical site visit or as a telehealth visit. If an in-person visit is done for non-COVID related symptoms, vital signs, physical examinations, and other procedures as needed may be done as requested by the Investigator.

Participants and their guardians will be instructed to monitor for respiratory/non-respiratory symptoms of COVID-19 during the study. In cases of suspected COVID-19 illness where the participant has not been evaluated at an offsite medical facility, they must contact the site within 3 days of symptom onset. If possible, the participant should have an in-person visit to help gather vital signs and do any necessary work up inclusive of physical examination. In cases where the participant has already been at an offsite facility, the site should endeavor to retrieve the visit notes. Only in situations where the participant cannot have an in-person visit should a telehealth visit be planned. Procedures for this visit are described in Section 6.1.2.8.2, and follow-up to confirm and assess the severity of the case of COVID-19 will be conducted at the next scheduled study visit.

6.1.1.3 COVID-19 Monitoring and Assessment of Severity

At each scheduled study visit, participants will be asked to report any PCR/rapid test confirmed cases of COVID-19 that occurred since last contact. Additional follow-up for any prior reported

cases of COVID-19 (ie, an unscheduled telehealth visit due to suspected COVID-19) will be conducted as well.

For all medically attended cases of COVID-19, an attempt will be made to obtain all medical records relevant to the COVID-19 healthcare visit and subsequent treatment in order to assess the severity of each case using the criteria provided in Appendix 3. Note, only the severity score should be recorded in the electronic case report form (eCRF).

All PCR/rapid test confirmed symptomatic cases of COVID-19 should also be recorded as an AE, SAE, or COVID-19 relevant AESI as appropriate.

Positive PCR swab results (performed in all participants at Day 0) in asymptomatic participants should also be entered as an AE.

6.1.2 Study Procedures

6.1.2.1 Screening Period

The following procedures will be performed within 14 days of study vaccination. The Screening visit and Day 0 visit may be combined, if feasible, at any given study site. Screening information collected as part of a standard-of-care protocol prior to informed consent form (ICF) signing may be used if collected during the same healthcare visit.

- Written informed consent will be obtained in conformance with Section 10.3 of this protocol.
- Review of medical history, including prior and concomitant medical conditions, recent vaccinations (≤ 90 days), and significant surgical procedures.
- Review of COVID-19 vaccination status, including number of prior vaccinations, vaccination type, and timing of most recent vaccination.
- Inclusion and exclusion criteria review via participant discussion and medical history review consistent with Section 4.1.1. Specific exclusions to study vaccination will be assessed before any vaccination. Waivers for enrolling participants with exclusions will not be given.
- Demographics, including age, year of birth, sex, race, ethnicity, weight, height, and body mass index (BMI; derived).
- Prior and concomitant medications, including recent and current medications at the time of screening to be reviewed to ensure eligibility criteria are fulfilled (see details in Section 7.4).
- Vital sign measurements, including respiratory rate, blood pressure, pulse rate, pulse oximetry, and temperature (oral or via forehead/ear reader).
- Baseline electrocardiogram (ECG)
- Urine pregnancy test for participants of childbearing potential only. A positive urine pregnancy test at Screening will result in screen failure.

- Physical examination to include head, eyes, ears, nose, and throat (HEENT), neck, lungs, heart, cardiovascular, abdomen, and musculoskeletal system/extremities to allow for study vaccination.
- Assessment of SAEs, starting from the time of informed consent.

6.1.2.2 Day 0 – On-site Study Vaccination

The Screening and Day 0 Visits may be combined whenever feasible. If these visits are not combined, then the following procedures need to be performed and recorded for Day 0. Participant eligibility must be confirmed prior to vaccination.

Prior to study vaccination, all participants with confirmed eligibility will have the following procedures performed:

- Inclusion and exclusion criteria review via participant discussion and medical history review consistent with Section 4.1.1. Specific exclusions to study vaccination will be assessed before any study vaccination.
- Prior and concomitant medications, including recent and current medications to be reviewed to ensure eligibility criteria are fulfilled (see details in Section 7.4).
- Vital sign measurements, including respiratory rate, blood pressure, pulse rate, pulse oximetry, and temperature (oral or via forehead/ear reader). On study vaccination days, vital sign measurements will be collected once before study vaccination to ensure participant has no evidence of fever prior to study vaccination.
- Urine pregnancy test for participants of childbearing potential only. A urine pregnancy test will be performed prior to study vaccination. A positive urine pregnancy test at any time will result in the participant not receiving any further study vaccination.
- Symptom-directed (targeted) physical examination. Physical examination must be done prior to study vaccination.
- Nasal swab (anterior nares) collection for SARS-CoV-2 PCR testing
- Oral swab for SARS-CoV-2 mucosal IgA-mediated hACE2 receptor-binding inhibition assay
- Blood sampling for immunogenicity tests:
  - SARS-CoV-2 (ELISA for anti-S-protein serology).
  - SARS-CoV-2 serostatus (anti-N-protein serology).
  - SARS-CoV-2 NAb assay.
  - Human angiotensin converting enzyme-2 (hACE2) receptor-binding inhibition assay.
- Randomization/Enrollment

At the time of study vaccination, the following procedures will be conducted for all randomized participants:

- Alcohol swab cleansing of the injection sites for study vaccine administration
- Vaccination with study vaccine as an intramuscular (IM) injection.
- Monitoring for any immediate hypersensitivity and anaphylaxis reactions. Participants will remain in clinic for at least 15 minutes post-vaccination for safety monitoring.
- Assessment of unsolicited AEs, MAAEs (all and related to study vaccination), any SAEs, and AESIs (including PIMMCs, myocarditis and/or pericarditis, and complications specific to COVID-19).

Following vaccination, participants will be trained to utilize an eDiary to record reactogenicity. All participants will be asked to record reactogenicity on the day of vaccination and for an additional 6 days after vaccination. Study site personnel should regularly review the eDiary for completeness. Should any reactogenicity event extend beyond 6 days after vaccination (toxicity grade ≥ 1), then it will be recorded using the Continuing Solicited AE form and followed to resolution per ICH guidelines for dataset capture. The toxicology grading scale implemented in the eDiary for the study is included in Appendix 2.

6.1.2.3 Day 28 – In-person/Home Health Care Follow-up Visit (-1 to + 7 Days)

All participants will have the following procedures performed on Day 28:

- Prior and concomitant medications (see details in Section 7.4).
- Oral swab for SARS-CoV-2 mucosal IgA-mediated hACE2 receptor-binding inhibition assay.
- Blood sampling for immunogenicity tests:
  - SARS-CoV-2 (ELISA for anti-S-protein serology).
  - SARS-CoV-2 serostatus (anti-N-protein serology).
  - SARS-CoV-2 NAb assay.
  - hACE2 receptor-binding inhibition assay.
- COVID-19 monitoring and assessment of severity.
- Assessment of unsolicited AEs, MAAEs (all and related to study vaccination), any SAEs, and AESIs (including PIMMCs, myocarditis and/or pericarditis, and complications specific to COVID-19).

6.1.2.4 Day 56 – Phone Follow-up Visit (± 7 Days)

All participants will have the following safety information collected via a remote visit (eg, phone call) on Day 56:

- Prior and concomitant medications (see details in Section 7.4).

- COVID-19 monitoring and assessment of severity
- Assessment of any SAEs, AESIs (including PIMMCs, myocarditis and/or pericarditis, and complications specific to COVID-19), and related MAAEs.

6.1.2.5 Day 90 – In-person/Home Health Care Follow-up Visit (± 7 Days)

All participants will have the following procedures performed on Day 90:

- Prior and concomitant medications (see details in Section 7.4).
- Symptom-directed (targeted) physical examination.
- Blood sampling for immunogenicity tests:
  - SARS-CoV-2 (ELISA for anti-S-protein serology).
  - SARS-CoV-2 serostatus (anti-N-protein serology).
  - SARS-CoV-2 NAb assay.
  - hACE2 receptor-binding inhibition assay.
- COVID-19 monitoring and assessment of severity
- Assessment of any SAEs, AESIs (including PIMMCs, myocarditis and/or pericarditis, and complications specific to COVID-19), and related MAAEs.

6.1.2.6 Day 118 – Phone Follow-up Visit (± 7 Days)

All participants will have the following safety information collected via a remote visit (eg, phone call) on Day 56:

- Prior and concomitant medications (see details in Section 7.4).
- COVID-19 monitoring and assessment of severity
- Assessment of any SAEs, AESIs (including PIMMCs, myocarditis and/or pericarditis, and complications specific to COVID-19), and related MAAEs.

6.1.2.7 Day 146 – Phone Follow-up Visit (± 15 Days)

All participants will have the following safety information collected via a remote visit (eg, phone call) on Day 146:

- Prior and concomitant medications (see details in Section 7.4).
- COVID-19 monitoring and assessment of severity
- Assessment of any SAEs, AESIs (including PIMMCs, myocarditis and/or pericarditis, and complications specific to COVID-19), and related MAAEs.

6.1.2.8 Unscheduled Visit

6.1.2.8.1 General Unscheduled Visit

General Unscheduled Visits not due to respiratory/non-respiratory symptoms suspected to be COVID-19 will be conducted by study personnel for safety follow-up for any participant experiencing a general medical issue while on study. During this visit, the principal investigator may also perform any of the assessments listed in the SOE (Table 1) including blood sample collection, physical assessments, or other optional testing if needed for the clinical evaluation of an AE.

- Prior and concomitant medications (see details in Section 7.4).
- Vital sign measurements, including respiratory rate, blood pressure, pulse rate, pulse oximetry, and temperature (oral or via forehead/ear reader).
- Full physical examination.
- Assessment of unsolicited AEs (only for Unscheduled Visits occurring through 28 days after last study vaccination), MAAEs (only related MAAEs should be recorded if more than 28 days after last vaccination), SAEs, and AESIs (including PIMMCs, myocarditis and/or pericarditis, and complications specific to COVID-19).
- Blood sample collection and other optional testing may be performed during an Unscheduled Visit if directed by the Investigator for clinical evaluation of an AE.

6.1.2.8.2 Unscheduled Visit Due to Suspected COVID-19

In cases of suspected COVID-19 illness where the participant has not been evaluated at an offsite medical facility, they must contact the site within 3 days of symptom onset. If possible, the participant should have an in-person visit to help gather vital signs and do any necessary work up inclusive of physical examination. In cases where the participant has already been at an offsite facility, the site should endeavor to retrieve the visit notes. Only in situations where the participant cannot have an in-person visit should a telehealth visit be planned.

For all telehealth visits:

- Prior and concomitant medications (see details in Section 7.4).
- Nasal swab (anterior nares) collection for SARS-CoV-2 PCR testing
- Assessment of unsolicited AEs (only for Unscheduled Visits occurring through 28 days after last study vaccination), MAAEs (only related MAAEs should be recorded if more than 28 days after last vaccination), SAEs, and AESIs (including PIMMCs, myocarditis and/or pericarditis, and complications specific to COVID-19).

6.1.2.9 Day 180 – End of Study In-person/Home Health Care Visit (± 15 Days)

All participants will have the following procedures performed on End of Study/In-Person Home

Health Care Visit.

- Prior and concomitant medications (see definitions in Section 7.4).
- Vital sign measurements, including respiratory rate, blood pressure, pulse rate, pulse oximetry, and temperature (oral or via forehead/ear reader).
- Symptom-directed (targeted) physical examination.
- Blood sampling for immunogenicity tests:
  - SARS-CoV-2 (ELISA for anti-S-protein serology).
  - SARS-CoV-2 serostatus (anti-N-protein serology).
  - SARS-CoV-2 NAb assay.
  - hACE2 receptor-binding inhibition assay.
- COVID-19 monitoring and assessment of severity
- Assessment of SAEs, AESIs (including PIMMCs, myocarditis and/or pericarditis, and complications specific to COVID-19), and related MAAEs.
- Completion of the EOS form.

6.2 Immunogenicity Assessments

Blood samples will be taken at the time points specified in the procedures above and in the SOEs (Section 1.1) to assess immune response (eg, IgG ELISA for anti-S protein serology, NAb assay, and hACE2 receptor-binding inhibition assay).

Oral swabs will be taken at the time points specified in the procedures above and in the SOEs (Section 1.1) to assess IgA mediated hACE2 receptor-binding inhibition.

hACE2 levels will be obtained at Day 0 and Day 28 from saliva biofluid samples to provide information about the mucosal IgA-mediated antibody response to SARS-CoV-2. The salivary gland epithelial cells express hACE2 and harbor a significant population of IgA-producing plasma cells. Secretory IgA in the saliva has been shown to have potent neutralizing activity against SARS-CoV-2 (Sheikh-Mohammed 2022).

The details on the handling, processing, and shipping of immunogenicity samples will be provided separately in a laboratory manual.

Participants will be asked to provide consent for the use of samples for future testing for assay development related to SARS-CoV-2 or other pathogens. Aliquots of all collected samples from this study may be retained for the stated purposes for a maximum of 25 years (starting from the date at which the last participant had the last study visit), unless local rules, regulations, or guidelines require different time frames or different procedures, in accordance with participant consent.

6.3 Discontinuation or Withdrawal

6.3.1 Individual Participants

6.3.1.1 Withdrawal from Study

Participants are free to withdraw from the study at any time upon request. Participation in the study may be stopped at any time at the discretion of the investigator or at the request of the Sponsor.

Participants may refuse further procedures (including study vaccination) but are encouraged to remain in the study for safety follow-up. In such cases where only safety is being conducted, participant contact could be managed via telemedicine contact (eg, telephone, web chat, video, FaceTime).

Any participant who withdraws from the study prematurely will undergo all EOS assessments at the time of withdrawal. The reason for the early EOS visit must be entered as withdrawal from study on the EOS form.

Vaccination with a non-study, approved or deployed SARS-CoV-2 vaccine alone will not be considered a reason for withdrawal from the study.

6.3.1.2 Replacement of Participants

Participants who sign the ICF but withdraw, are withdrawn or terminated from this study, or are lost to follow up prior to study vaccination may be replaced. Participants who receive study vaccine and subsequently withdraw, are discontinued from additional study visits, are terminated from the study, or are lost to follow-up will not be replaced.

6.3.1.3 Participants Lost to Follow-up

Whenever possible, any participant who withdraws from the study prematurely will undergo all EOS assessments. Any participant who fails to return for final assessments will be contacted by the site in an attempt to have them comply with the protocol.

All reasonable efforts, including contact of emergency contact, must be made to locate participants to determine and report their ongoing status. Lost to follow-up is defined by the inability to reach the participant after a minimum of 3 documented phone calls, text messages, faxes or emails (not performed on the same day), as well as a lack of response by the participant to one registered mail letter. All attempts should be documented in the participant's source documents and/or medical records. If it is determined that the participant has died, the study site will use permissible local methods to obtain the date and cause of death and as much other information as can be obtained, including post-mortem reports.

The status of participants who fail to complete final assessments will be documented in the eCRF. Data that would have been collected at subsequent visits will be considered missing.

6.3.1.4 Study Vaccination Pause Rules

Study vaccination will be paused in the event of reports of 2 or more events of probable or confirmed pericarditis or myocarditis (Table 5), pending review of cases by the Central Cardiac Adjudication Committee that will report the results of their adjudication to the Sponsor to determine whether enrollment may be resumed.

Adverse events meeting any one of the following criteria will result in a hold being placed on subsequent vaccinations pending further review by the Sponsor's Safety Monitoring Committee (SMC):

- One or more participant with an SAE considered related to the investigational vaccine by the investigator and by the Sponsor.
- Three or more participants with grade 3 (severe) single AE preferred term considered related to the investigational vaccine by the investigator and by the Sponsor.

In addition, any SAE assessed as related to vaccine (by study investigator and/or the Sponsor) will be reported to the Sponsor's SMC Chair as soon as possible, and within 24 hours of the Sponsor's awareness of the event. If a pause rule is met, the SMC will conduct a safety review within 48 hours of the identification of AEs meeting the pause rule definition. In addition, the SMC Chair will advise the Clinical Team to advise all sites to immediately pause enrolment and further dosing the study participants. An ad hoc Sponsor's SMC meeting will be convened to review the data and make alternative recommendations. The Sponsor's SMC Charter defines processes for how this review will occur and how the Chair's recommendations will be documented.

The Sponsor, along with medical monitor (Syneos), may request an SMC review for any safety concerns deemed clinically significant that may arise in the trial and not associated with any specific pause rule.

6.4 Study Termination

Although the Sponsor has every intention of completing the study, they reserve the right to discontinue it at any time for clinical or administrative reasons.

The EOS is defined as the date on which the last participant completes the last study visit (including the EOS visit and any additional long-term follow-up). Any additional long-term follow-up that is required for monitoring of the resolution of an AE or finding may be appended to the clinical study report.

7 STUDY INTERVENTIONS

Study vaccinations will comprise 1 IM injection with the study treatment assigned (Table 4).

Table 4: Investigational Treatments Used in This Study

Product	Section	Antigen Dose	Route	Manufacturer
NVX-CoV2601 coformulated Omicron XBB.1.5 SARS-CoV-2 rS vaccine with Matrix-M adjuvant	7.1.1	5 µg	IM	Serum Institute of India
Prototype/XBB.1.5 Bivalent Vaccine (Site-mixed NVX-CoV2373 + NVX-CoV2601) coformulated with Matrix-M adjuvant	7.1.2	5 µg (total)	IM	Serum Institute of India

Abbreviations: IM = intramuscular

7.1 Description of Products

7.1.1 NVX-CoV2601 (5 µg)

7.1.1.1 Formulation, Storage, Preparation, and Handling

NVX-CoV2601 (5 µg): Coformulated Omicron XBB.1.5 SARS-CoV-2 rS vaccine with Matrix-M adjuvant: supplied as a solution for preparation for injection, at a concentration of 10 µg antigen and 100 µg adjuvant per mL. All study vaccines must be stored according to the labelled instructions in a secure cabinet or room with access restricted to necessary clinic personnel. The study site will be required to keep a temperature log to establish a record of compliance with storage conditions.

The NVX-CoV2601 vaccine with Matrix-M adjuvant should be stored at 2°C to 8°C in a secured location. DO NOT FREEZE.

7.1.1.2 Dosing and Administration

The vaccine should be drawn into a syringe on the day of administration by a qualified member of study site personnel and should be administered according to standard practice by qualified study site personnel as directed in the Pharmacy Manual.

All injections will be administered in a 0.5 mL injection volume at a dose of 5 µg antigen with 50 µg Matrix-M adjuvant at each injection.

7.1.2 Prototype/XBB.1.5 Bivalent Vaccine (5 µg [Total])

7.1.2.1 Formulation, Storage, Preparation, and Handling

The bivalent vaccine containing antigen for the ancestral (Wuhan) SARS-CoV-2 strain and Omicron XBB.1.5 subvariant, will be prepared from study supplies of NVX-CoV2373 and NVX-CoV2601.

All study vaccines must be stored according to the labelled instructions in a secure cabinet or room with access restricted to necessary clinic personnel. The study site will be required to keep a temperature log to establish a record of compliance with storage conditions.

The vials for the preparation of the bivalent vaccine with Matrix-M adjuvant should be stored at 2°C to 8°C in a secured location. DO NOT FREEZE.

On the day of administration, the bivalent vaccine should be mixed according to the Pharmacy Manual in the clinic pharmacy or in an area designated for this function. All vaccines which are diluted or mixed in the study site clinic/investigational pharmacy should be used within 1 hour of being prepared and drawn into a syringe. For additional preparation, storage, and handling information for the bivalent vaccine, refer to the provided Pharmacy Manual.

7.1.2.2 Dosing and Administration

The bivalent vaccine should be prepared and drawn into a syringe on the day of administration by a qualified member of study site personnel and should be administered according to standard practice by qualified study site personnel as directed in the Pharmacy Manual.

All injections will be administered in a 0.5 mL injection volume at a dose of 5 µg total antigen (2.5 µg prototype antigen + 2.5 µg Omicron XBB.1.5 antigen) with 50 µg Matrix-M adjuvant at each injection.

7.2 Treatment Assignment and Bias Minimization

7.2.1 Treatment Allocation

An Interactive Web Response System (IWRS) will be responsible for the allocation of randomization numbers to individual participants. A copy of the randomization/enrollment code with true treatment allocations will be held by Syneos during the study. A separate open-label serialized list (containing carton/vial treatments) will be provided to clinical supplies for investigational medical product (IMP) packaging and labeling.

7.2.2 Randomization Strategy and Procedure

Randomization will take place on Day 0 after confirmation that the participant meets the inclusion/exclusion criteria.

Eligible participants will be randomized 1:1 to Group A or Group B (approximately 200 participants each). Randomization will be stratified by number of prior mRNA COVID-19 vaccinations received and site.

Within each study site, participants will be randomized to study treatment according to a list produced by Syneos. Prior to production, the randomization specification will be reviewed and

agreed to by the study team (the Sponsor and Syneos). Block size is considered potentially unblinding information and will only be known by unblinded study personnel.

7.2.3 Extent and Maintenance of Blinding

This is a double-blind study. To maintain the blind, predetermined unblinded study site personnel will manage vaccine logistics, preparation, and potentially administration according to the Pharmacy Manual so as to maintain the blind from the remainder of the study site personnel and participants. The unblinded study site personnel may administer study vaccine if qualified to do so but will not be involved in study related assessments or have participant contact for data collection after administration of study vaccine.

7.2.4 Unblinding Procedures

7.2.4.1 Planned Unblinding

A participant's vaccine assignment will not be revealed to the site study team until the end of the study. Participants will be informed about which product they received as soon as feasible after the end of the study.

7.2.4.2 Unplanned or Unintentional Unblinding

A participant's vaccine assignment will not be revealed to the site study team until the end of the study unless medical treatment of the participant depends on knowing the study vaccine the participant received. Should a situation arise where unblinding is required, the investigator at that study site has the sole authority to obtain immediate unblinding via the IWRS. Prior to unblinding, or as soon thereafter as possible, the investigator should contact the Syneos Medical Monitor to discuss the medical emergency and the reason for revealing the actual vaccine combination received by that participant. Emergency code breaks performed using the IWRS must be clearly explained and justified in the eCRF. The date on which the code was broken must also be documented.

When the investigator contacts the IWRS system to break a treatment code for a participant, they must provide the requested participant identifying information and confirm the necessity to break the treatment code for the participant. The investigator will then receive details of the study treatment for the specified participant and a blinded confirmation to document the unblinding will generate. The system will automatically inform the Sponsor and the Syneos Clinical Team via email that the code has been broken, but no treatment assignment will be communicated.

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the IWRS in case of emergency. The investigator will inform the participant how to contact their backup in cases of emergency when they are unavailable. The investigator will provide the protocol number, study vaccine name if available, participant number, and instructions for contacting the local entity which has responsibility for emergency code breaks to the participant

in case an emergency treatment code break is required at a time when the investigator and backup are unavailable.

7.3 Assessment and Verification of Compliance

All doses of the study vaccine should be administered in the clinical unit under direct observation of clinic personnel and recorded in the eCRF. Clinic personnel will confirm that the participant has received the entire dose.

The location (right or left arm, or other location if required), date, and timing of all doses of study vaccine will be recorded in the participants' eCRF. If a participant is not administered study vaccine, the reason for the missed dose will be recorded.

7.4 Prior and Concomitant Therapies

Administration of medications, therapies, or vaccines will be recorded in the eCRF. Prior medications include recent (≤ 90 days) and current medications and non-COVID-19 vaccinations. Concomitant medications will include all medications (including vaccines) taken by the participant Day 0 through EOS (or through the early termination visit if prior to that time). Prescription and over-the-counter (OTC) drugs will be included. Do not record herbals, vitamins, and supplements.

Receipt of any approved or authorized COVID-19 vaccine should also be recorded through EOS. Site staff will record the date(s) and brand of the approved or authorized SARS-CoV-2 vaccine combination received.

7.4.1 Prohibited Therapies

The following therapies are prohibited within the specified timeframes of study conduct except to the extent that they are required to treat an ongoing illness or to maintain the participants' health:

- No COVID-19 vaccines during the course of the study.
- No other vaccines (except for a licensed seasonal influenza vaccine as described in the next bullet or rabies, HPV, Td, TDaP, DTap, HBV, and meningococcal vaccines [if medically indicated]) will be allowed within 45 days prior to study vaccination or until 28 days after study vaccination.
- No influenza vaccine will be allowed within 14 days prior to study vaccination and within 14 days after study vaccination.
- No investigational product (drug/biologic/device) within 90 days prior to study vaccination until after the last study visit.

- No chronic administration (defined as > 14 continuous days) of any immunosuppressant medication within 90 days prior to study vaccination until the last study visit (except topical or intranasal steroids, or short-term oral steroids with course lasting ≤ 14 days). Topical tacrolimus and ocular cyclosporine are permitted. Rabies immune globulin should be administered if medically indicated.

8 SAFETY MONITORING

The timing and frequency of all safety assessments are listed in the SOE (Section 1.1).

Solicited and unsolicited AEs will be graded for severity using the provided criteria (Appendix 2). Recording of solicited and unsolicited AEs will be conducted by electronic data capture (EDC). AESIs, including PIMMCs, myocarditis and/or pericarditis, and complications specific to COVID-19, will also be monitored (see Appendix 1 for details).

A Central Cardiac Adjudication Committee has been established to adjudicate suspected myocarditis and/or pericarditis cases in the clinical development plan of NVX-CoV2373. Outcomes of the adjudications will be communicated to the Sponsor's Safety Monitoring Committee (SMC).

8.1 Definitions

- **Adverse event** – An AE is any untoward medical occurrence associated with the use of an intervention in humans whether or not it is considered intervention-related. Any abnormal laboratory test results or other safety assessments (eg, physical examination, vital signs measurements) that are clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease) will be considered AEs. An exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity, will be considered an AE.
- **Serious adverse event (SAE)** – An event is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

  – Death
  – A life-threatening AE (an event is considered "life-threatening" if, in the view of either the investigator or Sponsor, its occurrence places the patient or participant at immediate risk of death. It does not include an AE or suspected adverse reaction (AR) that, had it occurred in a more severe form, might have caused death.)
  – Inpatient hospitalization or prolongation of existing hospitalization. In general, hospitalization signifies that the participant has been detained, usually involving an overnight stay, at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an SAE.

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room (ER) or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

- **Causality or relatedness** – For each AE/SAE, the investigator must document in the medical notes that they have reviewed the AE/SAE and have provided an assessment of causality as follows.

  - Not Related: There is no reasonable possibility of relationship to study vaccine. The AE does not follow a reasonable temporal sequence from administration of study vaccine or can be reasonably explained by the participant's clinical state or other factors (eg, concurrent diseases, and concomitant medications).
  - Related: There is a reasonable possibility of relationship to study vaccine. The AE follows a reasonable temporal sequence from administration of study vaccine and cannot be reasonably explained by the participant's clinical state or other factors (eg, concurrent diseases or concomitant medications), represents a known reaction to study vaccine or other vaccines in its class, is consistent with the known pharmacological properties of the study vaccine, and/or resolves with discontinuation of the study vaccine (and/or recurs with re-challenge, if applicable).

- **Adverse reaction (AR)** – An AR is any AE caused by an IP.
- **Suspected adverse reaction (SAR)** – An SAR is any AE for which there is a reasonable possibility that the IP caused the AE. For the purposes of investigational new drug (IND) safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the IP and the AE. SAR implies a lesser degree of certainty about causality than AR.
- **Unexpected** – An event is considered unexpected if it is not listed in the IB, is not listed at the specificity or severity that has been observed, or, if an IB is not required or available, is not consistent with the risk information described in the General Investigational Plan or elsewhere in the IND. Unexpected also refers to events that are mentioned in the IB as occurring with a class of IPs or as anticipated from the pharmacological properties of the IP but are not specifically mentioned as occurring with the particular IP under investigation.

- **Severity or intensity** – The severity (or intensity) of an AE/SAE refers to the extent to which it affects the participant's daily activities and will be classified as mild, moderate, or severe using the following criteria:

  – Mild: These events require minimal or no treatment and do not interfere with the participant's daily activities.
  – Moderate: These events result in a low level of inconvenience or require minor therapeutic measures. Moderate events may cause some interference with normal functioning.
  – Severe: These events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

  If the severity of an AE/SAE changes, the most intense severity should be reported. An AE/SAE characterized as intermittent does not require documentation of the onset and duration of each episode. Grading criteria for specific AEs are provided in Appendix 2.

8.2 Documenting Adverse Events

At every study visit, participants will be asked to report any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and OTC medications).

In addition to participant observations, AEs will be documented from any data collected on the AE page of the eCRF or other documents that are relevant to participant safety.

Care will be taken not to introduce bias when detecting AEs, MAAEs, and SAEs. Open ended and non-leading verbal questioning of the participant is the preferred method to enquire about AE occurrences. AESIs will be inquired about according to the specific diseases listed in Appendix 1.

When an AE/SAE occurs, it is the responsibility of the investigator to review all available documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event. The investigator will then record all relevant AE/SAE information in the eCRF.

It is not acceptable for the investigator to send photocopies of the participant’s medical records in lieu of completion of the AE/SAE eCRF page. There may be instances when copies of medical records for certain cases are requested. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission. The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

The following variables will be recorded for each AE: verbatim/AE description and date for AE start and stop, severity, seriousness, causality, any other action taken, and the outcome. A new AE must be recorded if the severity of the AE changes.

Should an SAE have an outcome of death, the report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death.

8.2.1 Details of the Adverse Event

8.2.1.1 Assessment of Causality

There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data. The investigator may change their opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

The investigator should consider the following before reaching a decision on causality assessment:

- Time relationship between study vaccine injection and event's onset.
- Medical history.
- Study treatment.
- Mechanism of action of study vaccine.
- Class effect.
- Concomitant treatments in use.
- Withdrawal of study treatment.
- Lack of efficacy/worsening of existing condition.
- Possible vaccine enhancement of COVID-19.
- Erroneous treatment with study medication or concomitant medication.
- Protocol-related process.

8.2.1.2 Action Taken with Study Vaccine Due to Adverse Event

The action taken with study vaccine should be recorded using one of the following:

- Permanently discontinued/withdrawn (with date).
- Not applicable.

8.2.1.3 Other Action Taken

Details of any other actions taken should be specified:

- Specific therapy/medication.
- Surgical or medical procedure.

8.2.1.4 AE Outcome

Each AE should be rated according to one of the following outcomes:

- Recovered/resolved.
- Recovering/resolving.
- Not recovered/not resolved/ongoing.
- Recovered with sequelae/resolved with sequelae.
- Fatal.
- Unknown.

8.2.2 Time Frame for Collection

All AEs captured following the procedures listed in the SOE (Section 1.1) will be recorded on the AE page of the eCRF.

Medical occurrences that begin prior to study vaccination will be recorded on the Medical History/Current Medical Conditions section of the eCRF and not in the AE section.

All unsolicited AEs of any severity will be collected from the time of study vaccination through 28 days after vaccination.

All MAAEs will be collected through 28 days after vaccination and only treatment-related MAAEs will be collected after Day 28 until EOS.

All AESIs will be collected from the time of study vaccination until EOS.

All SAEs will be collected from signing of informed consent until completion of the EOS.

All vaccine administration errors, AEs, SAEs, cases of multisystem inflammatory syndrome, and all cases of COVID19 following vaccination must be reported per applicable local regulatory reporting guidance for safety events that occur in participants during the study if they meet the regulatory reporting criteria.

At any time after completion of the EOS visit, if an investigator learns of an SAE that could reasonably be considered related to study vaccine, they should promptly notify the Sponsor.

8.2.3 Classification of Events

8.2.3.1 Treatment-Emergent Adverse Events

Treatment-emergent adverse events are defined as any AE occurring or worsening on or after the study vaccination.

8.2.3.2 Adverse Events of Special Interest

Participants will be assessed for diagnosis of an AESI at all study contacts. AESIs include myocarditis and/or pericarditis, other PIMMCs, and complications specific to COVID-19 (listed in Appendix 1), or other potential AEs that may be determined at any time by regulatory authorities as additional information concerning COVID-19 is obtained. Listings of AESI are presented in Appendix 1.

An AESI must be reported as if it is an SAE (Section 8.3).

8.2.3.2.1 Myocarditis and/or Pericarditis (CDC Definition)

Participants reporting signs or symptoms of myocarditis or pericarditis (eg, fatigue, acute chest pain, shortness of breath, etc., see Table 5) within 4 weeks after vaccination should be evaluated as soon as possible by a physician who should initiate diagnostic work up including but not limited to laboratory tests and initial cardiac evaluation. If probable or confirmed myocarditis and/or pericarditis is diagnosed after the initial evaluation, all efforts will be made to route the participants to be followed up preferentially by a cardiologist or pediatric cardiologist (as applicable) who should complete the initial evaluation and manage cases following current practice guidelines (eg, AHA or other national/local guidelines); this might include performing functional cardiac evaluation and follow up of the case until resolution (see Table 6). A Central Cardiac Adjudication Committee has been established to adjudicate suspected myocarditis and/or pericarditis cases in the clinical development plan of NVX-CoV2373. Outcomes of the adjudications will be communicated to the SMC (when applicable) and to the Sponsor.

All myocarditis and/or pericarditis signs and symptoms, as well as all clinical evaluations, will be considered part of the study record and should be documented in the eCRF pages available to that end. Participants with confirmed myocarditis or pericarditis will be followed-up to document resolution of symptoms and/or abnormal test findings.

Table 5: Case Definitions of Probable and Confirmed Myocarditis, Pericarditis, and Myopericarditis

Condition	CDC Definition
Acute myocarditis	**PROBABLE:** Presence of ≥ 1 new or worsening of the following clinical symptoms:[1] • Chest pain, pressure, or discomfort • Dyspnea, shortness of breath, or pain with breathing • Palpitations • Syncope AND ≥ 1 new finding of • Troponin level above upper limit of normal (any type of troponin) • Abnormal ECG or rhythm monitoring findings consistent with myocarditis[2] • Abnormal cardiac function or wall motion abnormalities on echocardiogram • cMRI findings consistent with myocarditis[3] AND • No other identifiable cause of the symptoms and findings
	CONFIRMED: Presence of ≥ 1 new or worsening of the following clinical symptoms:[1] • Chest pain, pressure, or discomfort • Dyspnea, shortness of breath, or pain with breathing • Palpitations • Syncope AND ≥ 1 new finding of • Histopathologic confirmation of myocarditis[4] • cMRI findings consistent with myocarditis[3] in the presence of troponin level above upper limit of normal (any type of troponin) AND • No other identifiable cause of the symptoms and findings
Acute pericarditis[5]	Presence of ≥ 2 new or worsening of the following clinical features: • Acute chest pain[6] • Pericardial rub on exam • New ST-elevation or PR-depression on ECG • New or worsening pericardial effusion on echocardiogram or MRI
Myopericarditis	This term may be used for patients who meet criteria for both myocarditis and pericarditis.

Abbreviations: AV = atrioventricular; CDC = Centers for Disease Control and Prevention; cMRI = cardiac magnetic resonance imaging; ECG = electrocardiogram; ESC = European Society of Cardiology; MRI = magnetic resonance imaging.

1. Persons who lack the listed symptoms but who meet other criteria may be classified as subclinical myocarditis (probable or confirmed).
2. To meet the ECG or rhythm monitoring criterion, a probable case must include at least one of 1) ST-segment or T-wave abnormalities; 2) Paroxysmal or sustained atrial, supraventricular, or ventricular arrhythmias; or 3) AV nodal conduction delays or intraventricular conduction defects.

3. Using either the original or the revised Lake Louise criteria (Ferreira 2018).
4. Using the Dallas criteria (Aretz 1987). Autopsy cases may be classified as confirmed clinical myocarditis on the basis of meeting histopathologic criteria if no other identifiable cause.
5. Based on the 2015 ESC Guidelines for the diagnosis and management of pericardial diseases (Adler 2015). https://academic.oup.com/eurheartj/article/36/42/2921/2293375
6. Typically described as pain made worse by lying down, deep inspiration, or cough, and relieved by sitting up or leaning forward, although other types of chest pain might occur.

Adapted from Gargano 2021.

Table 6: Management of Probable or Confirmed Myocarditis, Pericarditis, and Myopericarditis Cases

Clinical Presentation	Procedures
Probable or Confirmed Myocarditis, Pericarditis or Myopericarditis	1) ER visit and evaluation by a physician (as per national/local guidelines): a. Diagnostic work up might include: i. CBC, Inflammatory markers: ESR, CRP ii. Cardiac markers: Troponin I, BNP, NT-proBNP iii. Chest radiograph iv. ECG 2) Evaluation by a cardiologist/pediatric cardiologist (as applicable) a. Follow AHA or other national/local guidelines i. Diagnostic work might include: 1. Stress test echocardiogram 2. Cardiac biopsy 3. cMRI 4. Other laboratory or cardiac assessment tests as applicable b. Follow up until resolution

Abbreviations: AHA = American Heart Association; BNP = brain natriuretic peptide; CBC = complete blood count; cMRI = cardiac magnetic resonance imaging; CRP = C-reactive protein; ECG = electrocardiogram; ER = emergency room; ESR = erythrocyte sedimentation rate; NT-proBNP = N-terminal pro b-type natriuretic peptide.

8.2.3.3 Medically Attended Adverse Events

An MAAE is defined as an AE that leads to an unscheduled visit to a healthcare practitioner.

8.2.3.4 Reactogenicity Symptoms

On the day of vaccination, participants will remain in clinic (or under observation) for at least 15 minutes to be observed for any immediate hypersensitivity and anaphylaxis reactions. Site specific local and general systemic reactogenicity reactions including start and stop dates will be recorded following vaccination.

Participants will utilize their eDiary to record reactogenicity following vaccination. All participants will be asked to record reactogenicity following vaccination on Day 0 and then daily for an additional 6 days after vaccination. Study site personnel should regularly review the

eDiary for completeness. Should any reactogenicity event extend beyond 6 days after vaccination, then it will be recorded using the Continuing Solicited AE form and followed to resolution per ICH guidelines for AE capture. Such AEs should be reported and managed as described in Section 8.3. The toxicology grading scale implemented in the eDiary for the study is included in Appendix 2.

8.3 Reporting Adverse Events

All SAEs must be reported according to ICH Good Clinical Practice (GCP) or local regulations, applying the regulation with the stricter requirements. Investigators and other study site personnel must inform appropriate Novavax representatives of any SAE that occurs during the course of the study, from the time of informed consent until the EOS visit, regardless of whether it is judged to be causally related to study vaccine or procedures. Notification must occur within 24 hours of when they become aware of it. AESIs, including PIMMC, myocarditis or pericarditis and complications specific to COVID-19 are to be reported within these timelines on the SAE/AESI Report form. The investigator should make every effort to obtain follow-up information on the outcome until the event is considered resolved, chronic and/or stable.

SAE reports received that may be attributed to both the study vaccine and an approved/authorized vaccine from a different manufacturer will be reported to local regulatory authorities as applicable. SAE reporting forms allow for the notation of other factors that may have impacted the investigator's assessment of causality. Investigators will be instructed to utilize this section of the reporting form to note the impact of an approved/authorized vaccine from a different manufacturer on the event, if applicable. Investigators will be required to report any SAEs in participants who received a different manufacturer's approved/authorized vaccine to local health care and/or regulatory authorities as per the local regulatory guidelines.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to Novavax Global Vaccine Safety within 24 hours as described above. The date when the AE becomes serious should be notated in the eCRF or on the SAE form.

All SAEs and AESI will also be recorded in the eCRF. The investigator is responsible for informing the Independent Ethics Committee (IEC)/IRB of the SAE as per local requirements. Paper SAE forms should be completed at the study site and emailed within 24 hours of study site awareness of the event to the Novavax Global Vaccine Safety mailbox:

[redacted]

The report form should be attached to the email; a notification email of the event describing it in the email text is not sufficient. There may be situations when an SAE has occurred, and the investigator has minimal information to include in the initial SAE report. However, it is very important that the investigator always makes an assessment of causality for every event prior to transmission of the SAE report form.

Minimum criteria for a reportable event are:

- Identifiable patient (participant number)
- A suspect product (ie, study vaccine)
- An identifiable reporting source (investigator/study site identification), and
- An event or outcome that can be identified as serious.

Follow-up information on SAEs must also be reported by the investigator within the same time frames.

8.3.1 Safety Reporting to Health Authorities, Independent Ethics Committees/Institutional Review Boards, and Investigators

Novavax or its designee will be responsible for notifications of SAEs and other qualifying events that are considered to be unexpected and related to study vaccine as expedited (eg, 7- or 15-Day reports to the relevant regulatory authorities and to participating investigators. In addition, Novavax or its designee will follow all applicable local and national regulatory requirements regarding safety reporting. Each investigator must comply with any applicable study local and national regulatory requirements related to the reporting of SAEs to the IRB/IECs responsible for reviewing the trial at their site, as well as the regulatory authority(ies) (where applicable).

Timelines and responsibilities (Novavax and its designee) for expedited and periodic safety reporting to the Health Authorities, Independent Ethics Committees/ Institutional Review Boards, and Investigators are provided in the Safety Management Plan as agreed by the Syneos designee and Novavax.

8.3.2 24/7 Medical Emergency Coverage for Urgent Protocol-related Medical Questions

In a study-related health emergency, when assigned medical monitors for a study cannot be reached by a caller, for discussion of urgent medical related questions an on-call physician can be reached 24 hours 7 days a week (24/7) via Syneos Call Center:

- Telephone: [redacted]

8.4 Pregnancy

Pregnancy is not considered an AE unless there is a suspicion that an investigational vaccine may have interfered with the effectiveness of a contraceptive medication. Any pregnancy that occurs during study participation must be reported using the Pregnancy Assessment form. To ensure participant safety, each pregnancy must be reported to Novavax Global Vaccine Safety within 24 hours of learning of its occurrence. If pregnancy occurs, further vaccination will be discontinued. Pregnancy must be followed up to determine outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and the status of both mother and child, even if the participant was discontinued from the study. Pregnancy

complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous miscarriages must be reported as an SAE.

Any pregnancy brought to the investigator's attention before the study is completed should be reported to Novavax Global Vaccine Safety using the Pregnancy Assessment form provided to sites.

Any pregnancy brought to the investigator's attention after the participant has completed the study but occurring while the participant was in the study must be promptly reported to:

Novavax Global Vaccine Safety: [redacted]

8.5 Overdose or Misuse

A drug overdose is defined as the accidental or intentional use of an IP or an administration error in an amount that is higher than is normally used. Every overdose must be reported to Novavax Global Vaccine Safety within 24 hours of awareness, using the details provided in Section 8.3 if the overdose was associated with an SAE. Other overdoses and those associated with non-serious AEs should be reported in the AE eCRF. Only overdoses associated with a clinical SAE need to be reported as an SAE. The quantity and details regarding the excess dose should be documented in the eCRF.

Overdose in this study is specifically defined as any dose greater than the intended protocol dose (Section 7). In case of overdose, it is recommended that the participant be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment be administered immediately. Note that administration of the "wrong" vaccine is a protocol deviation, but not, in the absence of associated AE, an SAE.

9 ANALYSIS

9.1 Sample Size Calculations

The sample size for this study is based on clinical and practical considerations and not on a formal statistical power calculation. The sample size is considered sufficient to evaluate the objectives of the study. With 200 participants in each treatment group, there is a greater than 99.9% probability to observe at least 1 subject with an AE if the true incidence of the AE is 5% and an 86.6% probability if the true incidence of the AE is 1%.

9.2 Analysis Sets

The following analysis sets are identified for analysis.

9.2.1 All Randomized Participants Analysis Set

The All Randomized Participants Analysis Set will include all participants who are randomized/enrolled, regardless of whether they actually received any study vaccine. The All Randomized Participants Analysis Set will be used for participant disposition summaries and will be analyzed according to the treatment as randomized/enrolled.

9.2.2 Full Analysis Set

The Full Analysis Set (FAS) will include all participants who are randomized/enrolled and received at least 1 dose of study vaccine, regardless of protocol violations or missing data. The FAS may be the secondary analysis set used for any immunogenicity analyses and will be analyzed according to the treatment as randomized.

9.2.3 Safety Analysis Set

The Safety Analysis Set will include all participants who provide consent, are randomized, and receive at least 1 dose of study vaccine. Participants in the Safety Analysis Set will be analyzed as actually treated.

9.2.4 Per-Protocol Analysis Set

The Per-Protocol (PP) Analysis Set will be determined for each strain, serology assay and study visit. The PP Analysis set will include all participants who receive the full prescribed regimen of the study vaccine up to the visit according to protocol, have serology results for baseline and the time point analyzed, are PCR negative at baseline for SARS-CoV-2, and have no major protocol violations or an event (eg, COVID-19 infection) that are considered clinically relevant to impact immunogenicity response as determined prior to database lock.

Within the PP Analysis Set there are 3 subsets defined:

9.2.4.1 Anti-S Protein IgG Serology Subset

All participants in the PP Analysis Set who are tested for anti-S protein IgG serology using ELISA at each timepoint will be included in this subset.

9.2.4.2 Neutralization Assay Subset

All participants in the PP Analysis Set who are tested using the neutralization assay at each timepoint will be included in this subset.

9.2.4.3 hACE2 Receptor-Binding Inhibition Assay Subset

All participants in the PP Analysis Set who are tested for hACE2 receptor-binding inhibition titers at each timepoint will be included in this subset.

9.2.4.4 Mucosal hACE2 Receptor Binding Inhibition Assay Subset

All participants in the PP Analysis Set who are tested for mucosal IgA-mediated hACE2 receptor binding inhibition titers at each time point will be included in this subset.

9.3 Analyses to be Performed

9.3.1 Safety Analysis

All safety analyses will be descriptive and conducted using the Safety Analysis Set. Listings will be provided for all safety parameters collected.

9.3.1.1 Solicited Adverse Events

The number and percentage of participants with solicited injection site and systemic AEs through 7 days after vaccination will be summarized overall and by vaccine group and by the worst maximum toxicity grade over 7 days. The durations of solicited local and systemic AEs after vaccination within the 7 Day diary period and entire safety follow-up period will also be summarized by vaccine group.

9.3.1.2 Unsolicited Adverse Events

Unsolicited AEs will be coded by system organ class (SOC) and preferred term (PT) using Medical Dictionary for Regulatory Activities (MedDRA).

Unsolicited AEs will be summarized according to the periods described in Section 8.2.2 both overall and by vaccine group and by SOC/PT, as well as by severity and relationship to the study vaccine to present the number and percentage with corresponding exact 95% CIs using the Clopper-Pearson method. For multiple occurrences of an adverse event in the same participant, a participant will be counted only once, using the most severe or most related occurrence for the summarization by severity or relationship to the study vaccine, respectively.

All MAAEs (only related MAAEs beyond 28 days following vaccination), AESIs (predefined list), and SAEs throughout the study (up to the time of pre-planned analyses) will be summarized overall and by vaccine group as well as by severity.

9.3.1.3 Prior and Concomitant Medications and Vaccinations

Prior and concomitant medications and vaccinations will be summarized overall and by vaccine group and preferred drug name as coded using the World Health Organization (WHO) drug dictionary for all participants on the Safety Analysis Set.

9.3.1.4 Extent of Exposure

The number of participants receiving study vaccine will be presented by vaccine group on the Safety Analysis Set. Below information will also be summarized by vaccine group: whether the vaccine is administered and the reason if not, whether the vaccine is administered per protocol and the reason if not, whether full dose is administered and the reason if not, anatomical location of the administration, follow-up time since the first vaccination.

9.3.1.5 Vital Sign Measurements and Physical Examination

Listings will be provided for vital sign measurements and physical examinations data collected.

9.3.2 Immunogenicity Analysis

All immunogenicity analyses will be descriptive. Listings will be provided for all immunogenicity data collected.

9.3.2.1 Analysis of Primary Immunogenicity Endpoints

The analysis of the primary immunogenicity endpoints will be performed using the Per-Protocol (PP) Analysis Set and the Neutralization Assay Subset.

The primary immunogenicity endpoints focus on NAb against the Omicron XBB1.5 strain at Day 28 following initial study vaccination. Neutralizing antibodies (NAb) GMT and GMFR (compared to Day 0) to the Omicron XBB.1.5 strain and corresponding 95% CIs, are summarized at Day 28 by vaccine group. GMT is calculated as the antilog of the mean of log-transformed titer values. GMFR is the antilog of the mean of log-transformed fold-rises. The 95% CIs are calculated based on the t-distribution of the log transformed titer or fold-rise values, then back transformed to the original scale. The between-group ratio of GMT (GMTR) at Day 28 and the two-sided 95% CIs are computed using the analysis of covariance with the vaccine group as the fixed effect and the titer at Day 0 (ie, adjusted for intergroup variation in baseline [pre-vaccination] titers) as the covariate. The mean difference between vaccine groups and the corresponding CI limits will then be exponentiated to obtain the ratio of NAb GMTs and the corresponding 95% CIs. There is no formal evaluation of statistical hypotheses.

Seroresponse is defined as post-vaccination titer ≥4-fold increase from baseline value. Participants with a baseline value below the lower limit of quantitation (LLOQ) will be considered achieving seroresponse only if the post-baseline value is greater than or equal to 4 times the LLOQ. The percentage of participants achieving seroresponse rate (SRR) is calculated at Day 28. 95% CIs of the SRR will be calculated based on the exact Clopper-Pearson method. Difference in SRR will be calculated at Day 28, with the 95% CI for the difference based on the method of Miettinen and Nurminen.

9.3.2.2 Analysis of Secondary Immunogenicity Endpoints

For the secondary immunogenicity endpoints of NAb response against the Omicron XBB.1.5 strain over time, analyses will be performed using the Per-Protocol (PP) Analysis Set and the Neutralization Assay Subset. NAb GMTs to the Omicron XBB.1.5 strain and 95% CIs are summarized at Day 0, 90, and 180. NAb GMFR (compared to Day 0) and SRR to the Omicron XBB.1.5 strain and 95% CIs are summarized at Day 90 and 180.

For the secondary immunogenicity endpoints of IgG antibody levels against the Omicron XBB.1.5 strain over time, analyses will be performed using the Per-Protocol (PP) Analysis Set and the Anti-S Protein IgG Serology Subset. IgG GMEUs to the Omicron XBB.1.5 strain and 95% CIs are summarized at Day 0, 28, 90, and 180. IgG GMFR (compared to Day 0) and SRR to the Omicron XBB.1.5 strain and 95% CIs are summarized at Day 28, 90 and 180.

Summary statistics used to evaluate secondary immunogenicity objectives are summarized by vaccine group. There is no formal evaluation of statistical hypotheses.

9.3.2.3 Analysis of Exploratory Immunogenicity Endpoints

For the exploratory immunogenicity endpoints of NAb and IgG antibody responses against the ancestral (Wuhan) strain over time, analyses will be performed using the Per-Protocol (PP) Analysis Set, and within the Neutralization Assay Subset and the Anti-S Protein IgG Serology Subset respectively. NAb GMTs and IgG GMEUs to the ancestral (Wuhan) strain with corresponding 95% CIs are summarized at Day 0, 28, 90, and 180. NAb and IgG GMFR (compared to Day 0) and SRR with corresponding 95% CIs are summarized at Day 28, 90 and 180. The endpoints will be analyzed by vaccine group.

For the exploratory immunogenicity endpoints of antibody responses in a hACE2 receptor binding inhibition assay against the Omicron XBB.1.5 and ancestral (Wuhan) strains over time, analyses will be performed using the Per-Protocol (PP) Analysis Set and the hACE2 Receptor-Binding Inhibition Assay Subset. Serum hACE2 GMTs to the Omicron XBB.1.5 and ancestral (Wuhan) strains with corresponding 95% CIs are summarized at Day 0, 28, 90, and 180. hACE2 GMFR (compared to Day 0) and SRR to the Omicron XBB.1.5 and ancestral (Wuhan) strains with corresponding 95% CIs are summarized at Day 28, 90 and 180. The endpoints will be analyzed by vaccine group.

Mucosal IgA-mediated hACE2 receptor inhibition assay responses to the Omicron XBB.1.5 and ancestral (Wuhan) strains will be summarized using the PP Analysis Set and the Mucosal hACE2 Receptor-Binding Inhibition Assay Subset. GMTs to the Omicron XBB.1.5 and ancestral (Wuhan) strains with corresponding 95% CIs will be summarized at Day 0 and Day 28. GMFR (compared to Day 0) and SRR with corresponding 95% CIs will be summarized at Day 28.

The other exploratory Immunogenicity analyses will be defined in the SAP.

9.3.3 Other Exploratory Analyses

The other exploratory analyses will be defined in the SAP.

9.4 Other Statistical Considerations

9.4.1 Population Analysis

9.4.1.1 Disposition and Protocol Compliance

The number of participants consented, randomized/enrolled, and vaccinated will be presented by vaccine group for the All Randomized Participants Analysis Set.

The number (percentage) of participants in the All Randomized Participants Analysis Set, FAS, Safety Analysis Set, and PP Analysis Set for the primary endpoint only who have completed the study up to the time of pre-planned analyses (including EOS for the final analysis) will be summarized by vaccine group.

The number (percentage) of participants who discontinue the study prior to EOS and the reason for discontinuation (eg, AE, investigator decision, lost to follow-up, non-compliance, etc.) will be presented by vaccine group.

The number (percentage) of participants with major protocol deviation(s) recorded throughout the study will be summarized by vaccine group and protocol deviation category.

9.4.1.2 Demographics and Baseline Characteristics

Baseline demographic and background characteristics (eg, age, gender, ethnicity, race, height, weight, and BMI [derived]) will be summarized by vaccine group for the FAS, Safety, and PP Analysis Sets. Frequencies and percentages will be presented for categorical variables. Continuous variables will be summarized using descriptive statistics (total number of participants, mean and standard deviation, median, minimum, and maximum).

Medical history will be coded using MedDRA terms. Baseline medical history recorded at Screening will be summarized by the study vaccine group and by MedDRA SOC/PT for all participants in the Safety Analysis Set. Within each SOC and PT, the number and percentage of participants with at least one medical history event will be presented, respectively. Multiple events within a given SOC and PT for a participant will be counted once.

The characterization of baseline immunity will be summarized, to include tabulation of PCR and anti-N results at Day 0, the brand(s) of mRNA vaccine previously received, the number of doses received, and the length of the interval between last mRNA vaccine and study investigational vaccine.

9.4.1.3 Listings of Population Analysis data

Listings of all data used for analysis of population parameters will be created.

9.5 Planned Interim Analyses

A formal interim analysis will be carried out when the complete data is available to evaluate the primary endpoint. A set of secondary and exploratory endpoints will also be analyzed at this time, dependent on the availability of data. The database extract is expected to include immunogenicity data and safety data through Day 28. An independent statistics organization or the internal statistics team will perform the analysis and receive unblinded data at the time of analyses, following final determination of participant exclusions from analysis populations and database extract. At the time of Day 28 data extract with receipt of the randomization list, the Sponsor will be unblinded at the participant level to prepare for regulatory submissions.

9.6 Specified Analyses for Independent Data Monitoring Committee Review

Data surrounding suspected cases of myocarditis/pericarditis will be provided to the appointed Central Cardiac Adjudication Committee as needed

9.7 Procedures for Reporting Changes to the Planned Analysis

Changes to the analyses or analysis methods specified in the protocol will be documented in the SAP and in the clinical study report.

10 ETHICAL CONSIDERATIONS

10.1 Good Clinical Practice

The investigator agrees that the study will be conducted according to the principles of ICH E6(R2). The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. The study will be conducted in compliance with the protocol, current GCP guidelines – adopting the principles of the Declaration of Helsinki – and all applicable regulatory requirements.

Prior to study initiation, the protocol and the informed consent documents will be reviewed and approved by the sponsor (or designee) and an appropriate ethics committee. Any amendment to the protocol or consent materials must also be approved by the study sponsor (or designee) and IRB and must be submitted/notified to the regulatory authority, as required, before they are implemented.

10.2 Ethics Review

Prior to the start of the study, the investigator is responsible for ensuring that the protocol and consent form have been reviewed and approved by a relevant IRB. The IRB shall be

appropriately constituted and perform its functions in accordance with ICH GCP and local requirements as applicable.

The IRB shall approve all protocol amendments (except for logistical or administrative changes), written informed consent documents and document updates, participant recruitment procedures (eg, advertisements), written information to be provided to the participants, IB, available safety information, information about payment and compensation available to participants, the investigator's curriculum vitae and/or other evidence of qualifications and any other documents requested by the IRB and Regulatory Authority (Competent Authority) as applicable.

10.3 Informed Consent

The nature and purpose of the study shall be fully explained to each participant. They must be informed that participation is voluntary.

Documentation of informed consent (either written or via eConsent) must be obtained from each participant prior to any study procedures being performed. The process of obtaining informed consent must be documented in the participant's source documents. The authorized person obtaining the informed consent must also sign the ICF, and a copy of the ICF must be provided to the participant. Participants must be re-consented to the most current version of the ICF during their participation in the study.

Participants will be requested to provide the name and contact information for an emergency contact and to provide consent for future testing to support establishment of correlates of protection against SARS-CoV-2 infection and disease (see Section 6.2 regarding sample retention).

The consent documents to be used for the study shall include all the elements of informed consent as outlined in accordance with ICH GCP and local requirements as applicable and be reviewed and approved by the appropriate IRB prior to use.

10.4 Data Privacy

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the sponsor, its designee, relevant regulatory authority(ies), or the IRB.

The investigator and all employees and co-workers involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

11 OVERSIGHT

11.1 Quality Control and Assurance

The Sponsor/designee shall implement and maintain quality control and quality assurance procedures with written standard operating procedures (SOPs) to ensure that the study is conducted and data are generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

This study shall be conducted in accordance with the provisions of the Declaration of Helsinki (October 2013) and ICH GCP (CPMP/ICH/135/95 and updates).

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB.
- Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures.

The investigator may not deviate from the protocol without a formal protocol amendment having been established and approved by an IRB, except when necessary to eliminate immediate hazards to the participant or when the change(s) involve(s) only logistical or administrative aspects of the study. Any deviations may result in the participant having to be withdrawn from the study and render that participant non-evaluable.

The identification and reporting of serious breaches of ICH GCP or the protocol to the Regulatory Authorities and Ethics Committees will be conducted according to local SOPs and regulations.

11.1.1 Monitoring

The Syneos clinical monitor, as a representative of the sponsor, is obligated to follow the study closely. In doing so, the monitor will visit the investigator and study site at periodic intervals as defined in the study monitoring and oversight plans in addition to maintaining necessary telephone and email contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and personnel.

All aspects of the study will be carefully monitored by the sponsor or its designee for compliance with applicable government regulation with respect to current ICH E6(R2)guidelines and standard operating procedures.

11.1.2 Audits

The investigator and institution involved in the study will permit study-related monitoring, audits, IRB review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the sponsor, their representatives, or the regulatory authority access to all study records.

The investigator should promptly notify the sponsor of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

11.1.3 Protocol Deviations

The investigator or designee must document and explain in the participant's source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change to, the protocol to eliminate an immediate hazard to study participants without prior IRB approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB for review and approval, to the sponsor for agreement, and to the regulatory authorities, if required.

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol. An important deviation (sometimes referred to as a major or significant deviation) is a subset of protocol deviations that leads to a participant being discontinued from the study or significantly affects the participant's rights, safety, or well-being and/or the completeness, accuracy, and reliability of the study data. An important deviation can include nonadherence to inclusion or exclusion criteria or nonadherence to regulatory authority including ICH E6(R2) guidelines.

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. The investigator will be notified in writing by the monitor of deviations. The IRB should be notified of all protocol deviations, as appropriate, in a timely manner.

Review and categorization of protocol deviations will occur prospectively during the study prior to database lock(s).

11.1.4 Records

11.1.4.1 Data Capture and Management

All required study data will be entered by study site personnel in the eCRF or by study participants in the eDiary created for the study. Data required according to this protocol will be recorded by study site personnel via data entry into the internet-based EDC software system or by study participant via the eDiary. The investigator shall ensure that all data from participant visits are promptly entered into the eCRFs in accordance with the specific instructions given. The investigator must sign each eCRF to verify the integrity of the data recorded. All internal

Syneos and external study site personnel seeking access to the eCRF are supported by a Service Desk (if applicable). At the end of the study all data captured electronically will be provided to the investigator on CD ROM for archiving at the study site.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

11.1.4.2 Source Documentation

The investigator must maintain source documents, such as laboratory reports, consultation reports, reactogenicity diaries and complete medical history and physical examination reports. All information in the CRF must be traceable to the participant's source documents.

The investigator/institution shall provide direct access to source data/documents for study related monitoring, audits, IRB review, and regulatory inspection.

11.1.4.3 Records Retention

The investigator/institution should maintain the study documents as specified in the ICH guidelines on GCP and as required by the applicable regulatory requirements. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

It is the Sponsor's responsibility to inform the investigator/institution as to when these documents no longer need to be retained.

11.2 Study Termination or Study Site Closure

Although the sponsor has every intention of completing the study, they reserve the right to discontinue it at any time for clinical or administrative reasons.

The end of the study is defined as the date on which the last participant completes the last study visit (including the EOS visit and any additional long-term follow-up). Any additional long-term follow-up that is required for monitoring of the resolution of an AE or finding may be appended to the clinical study report.

12 PUBLICATION POLICY

The Sponsor shall retain the ownership of all data. When the study is complete the Sponsor shall arrange the analysis and tabulation of data. A clinical study report shall then be prepared, which may be used for publication, presentation at scientific meetings or submission to regulatory authorities.

The Sponsor will generally support publication of multicenter studies only in their entirety and not as individual study site data. In this case, a coordinating investigator will be designated by

mutual agreement. Authorship will be determined by mutual agreement and in line with the International Committee of Medical Journal Editors authorship agreements. Authors will be provided reasonable access to all study data, statistical tables, figures, and relevant reports and will have the opportunity to review complete study results. All proposed publications based on this study must be participant to the Sponsor's approval requirements.

The Sponsor assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report, the results of this trial will be submitted for publication and/or posted in a publicly accessible database of clinical trial results.

13 FINANCING AND INSURANCE

The investigator is required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements required under US Title 21 CFR Part 54 and local regulations. In addition, the investigator must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither the sponsor nor the CRO nor the study site is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the sponsor nor the CRO nor the study site is financially responsible for further treatment of the disease under study.

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15 APPENDICES

APPENDIX 1: LISTINGS OF ADVERSE EVENTS OF SPECIAL INTEREST

Because it has been hypothesized that immunizations with or without adjuvant may be associated with autoimmunity, regulatory authorities have requested that Novavax instruct investigators to be especially vigilant regarding the PIMMCs listed in Table 7. Note that this regulatory request is not specific to Novavax's SARS-CoV-2 rS or Matrix-M adjuvant; and there is no current evidence to suggest that the study vaccines in this protocol are, or are not, associated with these illnesses. The list is not intended to be exhaustive, nor does it exclude the possibility that other diagnoses may be AESI.

Table 7: Potential Immune-Mediated Medical Conditions

Categories	Diagnoses (as MedDRA Preferred Terms)
Neuroinflammatory Disorders:	Acute disseminated encephalomyelitis (including site-specific variants: eg, non-infectious encephalitis, encephalomyelitis, myelitis, cranial nerve disorders including paralyses/paresis (eg, Bell's palsy), ascending flaccid paralysis, generalized convulsion, Guillain-Barre syndrome (including Miller Fisher syndrome and other variants), immune-mediated peripheral neuropathies and plexopathies (including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy), myasthenia gravis, multiple sclerosis, narcolepsy, optic neuritis, transverse myelitis, uveitis.
Musculoskeletal and Connective Tissue Disorders:	Antisynthetase syndrome, dermatomyositis, juvenile idiopathic arthritis (including Still's disease), connective tissue disorder, polymyalgia rheumatic, polymyositis, psoriatic arthropathy, polychondritis, rheumatoid arthritis, scleroderma (including diffuse systemic form and CREST syndrome), spondyloarthritis (including ankylosing spondylitis, reactive arthritis [Reiter's Syndrome], axial spondyloarthritis, juvenile spondyloarthritis and undifferentiated spondyloarthritis), systemic lupus erythematosus, systemic sclerosis, Sjogren's syndrome.
Vasculitides:	Large vessels vasculitis (including giant cell arteritis such as Takayasu's arteritis and temporal arteritis), medium sized and/or small vessels vasculitis (including polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg–Strauss syndrome [allergic granulomatous angiitis], Buerger's disease [thromboangiitis obliterans], Eosinophilic granulomatosis with polyangiitis, necrotizing vasculitis and ANCA-positive vasculitis [type unspecified], Henoch-Schonlein purpura, Behcet's syndrome).
Gastrointestinal Disorders:	Crohn's disease, celiac disease, ulcerative colitis, ulcerative proctitis.
Hepatic Disorders:	Autoimmune hepatitis, autoimmune cholangitis, cholangitis sclerosing primary biliary cirrhosis.
Renal Disorders:	Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis).

Table 7: Potential Immune-Mediated Medical Conditions

Categories	Diagnoses (as MedDRA Preferred Terms)
Cardiac Disorders:	Autoimmune myocarditis/cardiomyopathy. Myocarditis and/or pericarditis.
Skin Disorders:	Alopecia areata, psoriasis, vitiligo, Raynaud's phenomenon, erythema nodosum, autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis), cutaneous lupus erythematosus, morphoea, lichen planus, Stevens-Johnson syndrome.
Hematologic Disorders:	Autoimmune hemolytic anemia, immune thrombocytopenia, antiphospholipid syndrome, thrombocytopenia.
Metabolic Disorders:	Autoimmune thyroiditis, Basedow's disease, Hashimoto thyroiditis, diabetes mellitus type 1, Addison's disease.
Other Disorders:	Goodpasture syndrome, idiopathic pulmonary fibrosis, pernicious anemia, sarcoidosis.

Abbreviations: ANCA = anti-neutrophil cytoplasmic antibody; IgA = immunoglobulin A; MedDRA = Medical Dictionary for Regulatory Activities.
Source: Adapted from Tavares 2013.

Complications specific to COVID-19 are listed in Table 8. The list is not intended to be exhaustive, nor does it exclude the possibility that other diagnoses may be AESIs.

Table 8: Adverse Events Representing Complications Specific to COVID-19[1]

Categories	Diagnoses (as MedDRA System Organ Class/Preferred Term)
Respiratory/Infectious Disorders:	ARDS, pneumonitis, septic shock-like syndrome.
Cardiac Disorders:	Acute cardiac injury, arrhythmia, myocarditis, pericarditis (including myopericarditis).
Coagulopathy:	Deep vein thrombosis, myocardial infarction, stroke.
Renal Disorders:	Acute kidney injury.
Hematologic Disorders:	Thrombocytopenia, septic shock-like syndrome.
Inflammatory Disorders:	Cytokine Release Syndrome[2] related to COVID-19 infection, multisystem inflammatory syndrome in children (MIS-C).
Neurologic Disorders:	Generalized convulsions.

Abbreviations: ARDS = acute respiratory distress syndrome; COVID-19 = coronavirus disease 2019; DAIDS = Division of AIDS; MedDRA = Medical Dictionary for Regulatory Activities.

1. COVID-19 manifestations associated with more severe presentation and decompensation with consideration of enhanced disease potential. The current listing is based on Coalition for Epidemic Preparedness Innovations /Brighton Collaboration Consensus Meeting (12/13 March 2020) and expected to evolve as evidence accumulates (Lambert 2020).
2. Cytokine release syndrome is a disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath (DAIDS 2017).

APPENDIX 2: TOXICITY GRADING SCALE FOR CLINICAL ABNORMALITIES (LOCAL AND GENERAL SYSTEMIC REACTOGENICITY AND VITAL SIGNS)

Table 9: Modified FDA Toxicity Grading Scale for Clinical Abnormalities (Local and General Systemic Reactogenicity)

Local Reaction to Injectable Product				
	Mild (Grade 1)	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Pain	Does not interfere with activity	Repeated use of non-prescription pain reliever >24 hours or interferes with activity	Significant; any use of prescription pain reliever or prevents daily activity	Requires ER visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	Requires ER visit or hospitalization
Erythema/redness[a]	2.5 − 5 cm	5.1 − 10 cm	>10 cm	Necrosis or exfoliative dermatitis[b]
Induration/swelling[a]	2.5 − 5 cm	5.1 − 10 cm	>10 cm	Necrosis[b]
Systemic (General)				
	Mild (Grade 1)	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Fever[c] (°C) (°F)	38.0 − 38.4 100.4 − 101.1	38.5 − 38.9 101.2 − 102.0	39.0 − 40 102.1 − 104	>40 >104
Nausea/vomiting	Does not interfere with activity or 1 − 2 episodes/24 hours	Some interference with activity or >2 episodes/24 hours	Prevents daily activity, or requires IV hydration outside of hospital	Requires ER visit or hospitalization
Headache	Does not interfere with activity	Repeated use of non-prescription pain reliever >24 hours or interferes with activity	Significant; any use of prescription pain reliever or prevents daily activity	Requires ER visit or hospitalization
Fatigue/Malaise	Does not interfere with activity	Some interference with activity	Significant, prevents daily activity	Requires ER visit or hospitalization
Myalgia	Does not interfere with activity	Some interference with activity	Significant, prevents daily activity	Requires ER visit or hospitalization
Arthralgia	Does not interfere with activity	Some interference with activity	Significant, prevents daily activity	Requires ER visit or hospitalization

[a] The measurements should be recorded as a continuous variable.

[b] These events are not participant reported through the eDiary and will be monitored through the AE pages of the study database.

[c] Oral temperature if participant collected, sites may collect temperature using local clinic practices/devices. Toxicity grade will be derived.

Source: FDA 2007

Table 10: FDA Toxicity Grading Scale for Clinical Abnormalities (Vital Signs)

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Tachycardia (bpm)	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia (bpm)[a]	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) (mm Hg)	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) (mm Hg)	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) (mm Hg)	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate (breaths per minute)	17 – 20	21 – 25	> 25	Intubation

Note: Participant should be at rest for all vital sign measurements.

[a] When resting heart rate is between 60 – 100 bpm. Use clinical judgement when characterizing bradycardia among some healthy participant populations (eg, conditioned athletes).

Source: FDA 2007

APPENDIX 3: ASSESSMENT OF COVID-19 SEVERITY

Table 11: COVID-19 Severity Grading Criteria

Grade	Criteria
Mild	≥ 1 of the following: • Fever (defined by subjective or objective measure, regardless of use of anti-pyretic medications) • New onset cough ≥ 2 additional COVID-19 symptoms: • New onset or worsening of shortness of breath or difficulty breathing compared to baseline. • New onset fatigue. • New onset generalized muscle or body aches. • New onset headache. • New loss of taste or smell. • Acute onset of sore throat, congestion, or runny nose. • New onset nausea, vomiting or diarrhea.
Moderate	≥ 1 of the following: • High fever (≥ 38.4°C) for ≥ 3 days (regardless of use of anti-pyretic medications, need not be contiguous days). • Any evidence of significant lower respiratory tract infection (LRTI): • Shortness of breath (or breathlessness or difficulty breathing) with or without exertion (greater than baseline). • Tachypnea: 24 to 29 breaths per minute at rest. • SpO_2: 94% to 95% on room air. • Abnormal chest X-ray or chest computerized tomography (CT) consistent with pneumonia or LRTI. • Adventitious sounds on lung auscultation (eg, crackles/rales, wheeze, rhonchi, pleural rub, stridor).
Severe	≥ 1 of the following: • Tachypnea: ≥ 30 breaths per minute at rest. • Resting heart rate ≥ 125 beats per minute. • SpO_2: ≤ 93% on room air or PaO_2/FiO_2< 300 mmHg. • High flow oxygen (O_2) therapy or non-invasive ventilation (NIV)/non-invasive positive pressure ventilation (NIPPV) (eg, continuous positive airway pressure [CPAP] or bilevel positive airway pressure [BiPAP]). • Mechanical ventilation or extracorporeal membrane oxygenation (ECMO). One or more major organ system dysfunction or failure to be defined by diagnostic testing/clinical syndrome/interventions, including any of the following: • Acute respiratory failure, including acute respiratory distress syndrome (ARDS). • Acute renal failure. • Acute hepatic failure. • Acute right or left heart failure.

Table 11: COVID-19 Severity Grading Criteria

Grade	Criteria
	• Septic or cardiogenic shock (with shock defined as systolic blood pressure [SBP] < 90 mm Hg OR diastolic blood pressure [DBP] < 60 mm Hg). • Acute stroke (ischemic or hemorrhagic). • Acute thrombotic event: acute myocardial infarction (AMI), deep vein thrombosis (DVT), pulmonary embolism (PE). • Requirement for: vasopressors, systemic corticosteroids, or hemodialysis. • Admission to an intensive care unit (ICU). • Death.