A Randomized, Observer-Blinded, Phase 3 Study to Compare the Immunogenicity and Safety of 3 Lots of NVX-CoV2373 in Adults

Investigational Product	NVX-CoV2373
Protocol Number	2019nCoV-307
Clinical Trial Registry Identifiers	NCT05463068
Version Number	5.0
Version Date	July 20, 2022
Amendment	Amendment 4
Indication Studied	Prevention of COVID-19 caused by SARS-CoV-2
Sponsor	Novavax, Inc 21 Firstfield Road Gaithersburg, MD 20878 United States

Confidentiality Statement

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 of Technical Requirements for Pharmaceuticals for Human Use (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 Randomized, Observer-Blinded, Phase 3 Study to Compare the Safety, and Immunogenicity of 3 Lots of NVX-CoV2373 in Adults
Protocol Number	2019nCoV- 307
Version Number	5.0
Version Date	July 20, 2022

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:**	
[redacted]	[redacted]	
Clinical Operations Representative		
Name:	**Title:**	
[redacted]	[redacted]	

INVESTIGATOR'S AGREEMENT

I have read the protocol, appendices, and accessory materials related to Study 2019nCoV-307 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**

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LIST OF ABBREVIATIONS

Abbreviation	Definition
24/7	24 hours 7 days a week
AE	Adverse event
AESI	Adverse event of special interest
ANCA	Anti-neutrophil cytoplasmic antibody
ANCOVA	Analysis of covariance
ARDS	Acute respiratory distress syndrome
ATC	Anatomical therapeutic chemical
BAL	Bronchoalveolar lavage
BMI	Body mass index
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CRO	Clinical research organization
DAIDS	Division of AIDS
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
ELISA	Enzyme-linked immunosorbent assay
EoS	End of Study
ER	Emergency room
FAS	Full Analysis Set
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMEU	Geometric mean ELISA unit
GMFR	Geometric mean fold rise
GMT	Geometric mean titer
GMTR	Between-group ratio of MN_{50} GMTs
hACE2	Human angiotensin-converting enzyme 2
HEENT	head nose ears and throat
HREC	Human Research Ethics Committee
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IM	Intramuscular

Abbreviation	Definition
IND	Investigational New Drug
IRB	Institutional Review Board
IWRS	Interactive Web Response System
MAAE	Medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East Respiratory Syndrome
MHC	Major histocompatibility complex
MN_{50}	Microneutralization assay with an inhibitory concentration of 50%
OTC	Over the counter
PCR	Polymerase chain reaction
PIMMC	Potential immune-mediated medical conditions
PP	Per-Protocol
PT	Preferred term
Rs	Recombinant spike
S	Spike (protein)
SAE	Serious adverse event
SAR	Serious adverse reaction
SARS-CoV	Severe acute respiratory syndrome coronavirus
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SCR	Seroconversion rate
sgRNA	Subgenomic RNA
SII	Serum Institute of India
SOC	System organ class
SOE	Schedule of Events
SOP	Standard Operating Procedure
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
Th1	Type 1 T helper
US	United States

1 SYNOPSIS

<table>
<tr><td>Title</td><td>A Randomized, Observer-Blinded, Phase 3 Study to Compare the Immunogenicity and Safety of 3 lots of NVX-CoV2373 in Adults</td></tr>
<tr><td>Short Title</td><td>Phase 3 lot consistency study for NVX-CoV2373</td></tr>
<tr><td>Phase</td><td>Phase 3</td></tr>
<tr><td>Study Design</td><td>This is a randomized, Phase 3 study comparing the immunogenicity and safety of 3 different lots of Novavax vaccine with Matrix-M™ adjuvant (NVX-CoV2373). The study will enroll approximately 900 previously vaccinated adults 18 to 49 years of age, inclusive.
Participants will be screened at baseline with the goal of enrolling approximately 900 previously vaccinated participants. Participants will be randomized 1:1:1 to receive 1 dose of the vaccine from 1 of 3 different lots, given on Day 1, at a dose level of 5 µg of antigen with 50 µg of Matrix-M adjuvant.
All participants will remain on study for immunogenicity and safety data collection through 28 days following the vaccination.</td></tr>
<tr><td>Study Rationale</td><td>Novavax, Inc. has developed a recombinant vaccine adjuvanted with the saponin-based Matrix-M adjuvant (NVX-CoV2373) for the prevention of disease caused by SARS-CoV-2.
The purpose of this study is to compare the consistency of immunogenicity and safety of 3 different lots of NVX-CoV2373 in previously vaccinated adult participants 18 to 49 years of age. Data from the study are intended to support the overall manufacturing consistency data submitted as part of regulatory submissions in the United States (US) and elsewhere, as needed.</td></tr>
<tr><td>Target Population</td><td>Medically stable male and non-pregnant females 18 to 49 years of age, inclusive, who have been previously vaccinated against SARS-CoV-2.</td></tr>
<tr><td>Treatment Groups</td><td>Total number of participants planned: Approximately 900
Total number per vaccine group:
<table>
<tr><th>Vaccine</th><th>Age (years)</th><th>Baseline Serostatus</th><th>Number of doses</th><th>Number of participants</th><th>Dose (antigen/ Matrix-M adjuvant)</th></tr>
<tr><td>Lot 1 (Group 1)</td><td rowspan="3">18 to 49</td><td rowspan="3">Previously vaccinated</td><td>1</td><td>300</td><td>5µg / 50 µg</td></tr>
<tr><td>Lot 2 (Group 2)</td><td>1</td><td>300</td><td>5µg / 50 µg</td></tr>
<tr><td>Lot 3 (Group 3)</td><td>1</td><td>300</td><td>5µg / 50 µg</td></tr>
</table></td></tr>
<tr><td>Length of Participation</td><td>On study (including screening and follow-up): up to 2 months.</td></tr>
<tr><td>Intervention</td><td>NVX-CoV2373 (5 µg): Prototype SARS-CoV-2 rS. Vaccine supplied as a solution for preparation for injection, at a concentration of 10 µg antigen and 100 µg Matrix-M adjuvant per mL. The NVX-CoV2373 vaccination regimen will comprise 1 intramuscular (IM) injection (Day 1) of 0.5 mL injection volume at a dose of 5 µg antigen. Three different lots will be used in the study.</td></tr>
<tr><td>Primary Objective and Endpoint</td><td>Hypothesis: Immunoglobulin G (IgG) antibody responses following 1 dose of vaccine will be equivalent across the 3 lots evaluated.</td></tr>
</table>

	Objective: To demonstrate the equivalence of 3 different vaccine lots based on IgG responses. Endpoint: • IgG geometric mean enzyme-linked immunoassay (ELISA) unit (GMEU) concentrations (ie, GMEU/mL) to the SARS-CoV-2 spike protein at Day 29 in each treatment arm; equivalence will be demonstrated if the 95% confidence intervals [CIs] of GMEU concentrations for all pairs of lots are within the pre-specified equivalence range of 0.67 to 1.5 GMEU/mL .
Secondary Objectives and Corresponding Endpoints	Objective: To characterize the IgG antibody responses to 3 different lots of NVX-CoV2373. Endpoint: • Proportion of participants in each treatment arm who achieve seroconversion (≥ 4-fold increase from baseline) in IgG concentrations to the SARS-CoV-2 spike protein at Day 29. Objective: To characterize the neutralizing antibody responses to 3 different lots of NVX-CoV2373. Endpoints: • Microneutralization (MN) assay with inhibitory concentrations of 50% (MN_{50}) geometric mean titers to the SARS-CoV-2 spike protein at Day 29 in each treatment arm. • Proportion of participants in each treatment arm who achieve seroconversion (≥ 4-fold increase from baseline) in MN assay with MN_{50} titers to the SARS-CoV-2 spike protein at Day 29. Objective: To characterize antibody responses in a human angiotensin-converting enzyme 2 (hACE2) receptor binding inhibition assay to the SARS-CoV-2 spike protein in participants vaccinated with 3 different lots of NVX-CoV2373. Endpoints: • hACE2 inhibition assay titers (geometric mean titers [GMTs]) at Day 29in each treatment arm. • Proportion of participants in each treatment arm who achieve seroconversion (≥ 4-fold increase from baseline) in hACE2 titers to the SARS-CoV-2 spike protein at Day 29. Objective: To compare the overall safety of 3 different lots of NVX-CoV2373. Endpoints: • Incidence, duration, severity, and relationship of medically attended adverse events (MAAEs) and adverse events of special interest (AESIs) (including myocarditis and/or pericarditis) through Day 29 (ie, 28 days after the vaccine dose). • Incidence and relationship of serious adverse events (SAEs) throughout the study.
Exploratory Objectives and Corresponding Endpoints	Objective: To utilize additional assays (current or to be developed) to best characterize the immune response for future vaccine development needs. Endpoint: Additional endpoints to compare immune responses may be developed based on the assays used.

Number of Sites	Approximately 30 sites in the US
Study Duration	Estimated duration: 1 Month (excluding screening)

1.1 Schedule of Events

The Schedule of Events (SOE) is presented in Table 1.

Table 1 Schedule of Events

Study Day	–30 to 1[1]	1[1]	Unscheduled visit	29
Window (days)	–	–		+ 4
Study Visit	Screening	1		EOS[2]
Informed consent	X			
Medical history[3]	X			
Inclusion/exclusion criteria[4]	X	X[4]		
Demographics	X			
Prior/concomitant medications	X[5]	X[6]	X	X
Vital sign measurements	X	X[6]	X	X
Urine pregnancy test (WOCBP)	X	X[6]		
Physical examination	X	X[6]	X	X
Baseline ECG		X[6]		
Nasal swab at clinic for SARS-CoV-2 (PCR) – anterior nares		X[6]		
Blood sampling for SARS-CoV-2 (ELISA for anti S-protein serology, MN_{50} assay, and hACE2 receptor-binding inhibition assay)		X[6]		X
Randomization		X[6]		
Vaccination		X[7]		
SAEs	X	X	X	X
All MAAEs and AESIs (including PIMMCs, myocarditis or pericarditis])[8]		X	X	X
EOS form[9]				X

Abbreviations: AESI = adverse event(s) of special interest; ELISA = enzyme-linked immunosorbent assay; EOS = end of study; hACE2 = human angiotensin-converting enzyme 2; MAAE = medically attended adverse event; MN_{50} = microneutralization assay with an inhibitory concentration of 50%; PCR = polymerase chain reaction; PIMMC = potential immune-mediated medical conditions; S = spike (protein); SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WOCBP = women of childbearing potential.

1. The Screening visit and Day 1 visit may be combined if feasible at any given study site.
2. EOS assessments will be conducted via on-site visit. Should participants decide to terminate early, a telephone call may occur to collect the maximum safety data possible.
3. Significant medical history should be recorded, including prior and ongoing medical conditions and significant surgical procedures.
4. Specific exclusions to study vaccination will be assessed before any vaccination. Waivers to enrolling participants with exclusions will not be given.
5. Recent (≤ 90 days) and current medications, including non-COVID-19 vaccines, should be recorded in the concomitant medication eCRF. All COVID-19 vaccines administered prior to screening should be recorded in the vaccine history eCRF.
6. Performed prior to study vaccination.
7. On vaccination day, 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 reactions.
8. Recording of SAEs, MAAEs, and AESIs (including potential immune-mediated medical conditions [PIMMCs] and myocarditis or pericarditis). See Table 4 for symptoms of myocarditis or pericarditis and Section 8.2.3.6 for instructions for follow-up.
9. EOS form will be completed for all participants, including participants who are terminated early.

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). Nearly two years later, SARS-CoV-2 transmission remains high, partly due to the emergence of multiple variant strains of the virus. The World Health Organization (WHO) situation report from 09 February 2022 identified 399,600,607 confirmed cases and 5,757,562 deaths globally (WHO 2022).

The present study aims to compare the immunogenicity and safety of 3 lots of NVX-CoV2373 in adults.

2.1.1 Description of NVX-CoV2373

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 in adults 18 years of age and older. 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. The S protein from each virus is a type 1 trimeric GP that is produced as an inactive S0 precursor. The S-gene was codon-optimized for expression in *Spodoptera frugiperda* (Sf9) insect cells.

All SARS-CoV-2 rS vaccines are adjuvanted with Matrix-M adjuvant. 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 (APCs), 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.

Additional product information including manufacturing details, supportive clinical and nonclinical study summaries can be found in the SARS-CoV-2 rS Investigator's Brochure (IB) (Novavax 2021).

2.1.2 Supportive Nonclinical Data

Supportive nonclinical data are available through studies conducted using Novavax manufactured SARS-CoV-2 rS products. Pharmacological properties of the SII-produced vaccines used in this study are expected to be equivalent to those produced by Novavax.

2.1.2.1 Pharmacology

2.1.2.1.1 NVX-CoV2373 Nonclinical Overview

Mouse immunogenicity studies were conducted to evaluate several SARS-CoV-2 S protein variants and select the vaccine candidate (Tian 2020). The selected vaccine candidate, BV2373 (3Q-2P), was demonstrated to be immunogenic and elicited functional antibodies. For the tested constructs, shallow dose responses with Matrix-M adjuvant were observed, suggesting that the adjuvant may be significantly antigen-sparing in large animals and humans.

The candidate SARS-CoV-2 rS vaccine, based on the BV2373 construct (NVX-CoV2373), has been evaluated in dose titration studies in hamsters, cynomolgus macaques, rhesus macaques, and baboons. In hamsters, two-dose regimens with 1 or 10 µg SARS-CoV-2 rS/15 µg Matrix-M adjuvant were highly immunogenic, resulting in high anti-S immunoglobulin G (IgG) titers and high hACE2 binding inhibition titers in a shallow dose-dependent manner, suggestive of dose-sparing. Of note, anti-S IgG levels and human angiotensin-converting enzyme (hACE2) binding inhibition titers were highly correlated. In cynomolgus macaques, two-dose regimens of 5 or 25 µg SARS-CoV-2 rS/25 or 50 µg Matrix-M adjuvant were also highly immunogenic, resulting in high anti-S IgG levels, high hACE2 binding inhibition titers, and high neutralizing antibody responses. The 5 and 25 µg antigen doses gave generally similar responses when administered twice with 50 µg of Matrix-M adjuvant.

In rhesus macaques, 5 or 25 µg doses of SARS-CoV-2 rS were administered with 50 µg of Matrix-M adjuvant in one-dose or two-dose regimens, the latter at a 21-day interval. All active regimens elicited anti-S IgG, hACE2 binding inhibition, and neutralizing antibody responses, but antibody titers were approximately 20-30-fold higher after completion of the two-dose regimens. Antigen dose had little impact on immunogenicity in either one- or two-dose regimens.

Virus challenge studies were performed in mice, hamsters, and cynomolgus and rhesus macaques. In 2 mouse challenge models, immunization with 1 or 2 doses of SARS-CoV-2 rS/ Matrix-M adjuvant suppressed viral replication, reduced lung inflammation, and reduced systemic morbidity (weight loss) after SARS-CoV-2 live virus challenge and were not associated with any obvious exacerbation of the inflammatory response to the virus or worsening of clinical outcomes. The best responses were seen in animals receiving 2 doses of adjuvanted vaccine. Similar protection (weight loss and activity level) against live virus challenge was seen in hamsters, a SARS-CoV-2 permissive species due to the presence of an ACE2 receptor with close

homology to the human molecule. Protection has been demonstrated in hamsters challenged both by direct inoculation and also by cohabitation with unimmunized SARS-CoV-2-infected animals.

2.1.2.1.2 Baboon SARS-CoV-2 Recombinant Spike Protein Immunogenicity Study NVX 702-087

In baboons, which may be more predictive of responses in humans, 5 and 25 µg SARS-CoV-2 rS/50 µg Matrix-M adjuvant induced high levels of anti-S IgG, hACE2-binding inhibiting antibodies, and neutralizing antibodies. Matrix-M adjuvant provided antigen-sparing effects and supported induction of functional antibodies. Importantly, Matrix-M-adjuvanted SARS-CoV-2 rS also appeared to induce strong Th1 CD4+ T-cell responses to SARS-CoV-2 S protein that included polyfunctional effector phenotypes. Current data in this small baboon study confirms that doses of 5 µg and 25 µg with 50 µg Matrix-M adjuvant were the correct doses to test clinically, with Matrix-M adjuvant appearing critical for maximum responses. This finding was confirmed in a Phase 1 trial in humans (Keech 2020).

2.1.2.1.3 SARS-CoV-2 rS Challenge of Cynomolgus Macaques Immunized in Study NVX 702-094

Cynomolgus macaques administered with human doses of 5 or 25 µg SARS-CoV-2 rS adjuvanted with 50 µg Matrix-M adjuvant had high and comparable levels of anti-S IgG titers and hACE2 receptor binding inhibition titers detected 21 days after the first immunization. All of the macaques immunized with any dose or regimen of SARS-CoV-2 rS/Matrix-M adjuvant were protected against live virus challenge, as evidenced by the reduction of total viral RNA and subgenomic RNA (sgRNA) to below the limit of quantitation in bronchoalveolar lavages (BALs) and nasal swabs.

Combined nasal and intratracheal challenge of immunized rhesus macaques showed reduction of nasal wash total SARS-CoV-2 RNA in all immunized animals relative to placebo-treated macaques as early as Day 2 post-challenge, and clearance of total viral RNA to below detectable limits in 90% of two-dose animals by Day 7 or 8. In BAL fluid, similar reductions in total viral RNA were noted and all two-dose animals cleared viral RNA by Day 4 post-challenge, as did 90% of single-dose animals by Day 7 or 8. Considering sgRNA, believed to be a better marker of active viral replication, a similar pattern was noted. Animals immunized with 2 doses of SARS-CoV-2 rS with Matrix-M adjuvant cleared sgRNA from their nasal wash by Day 4 and had no detectable sgRNA in BAL fluids at any time. sgRNA reductions were less in animals immunized with 1 dose only, but sgRNA load were still markedly less than in placebo animals. No challenged animal in any vaccine group, regardless of completeness of protection, had any Evidence of vaccine-enhanced disease.

2.1.2.2 Toxicology

A Good Laboratory Practice (GLP)-compliant toxicity study in New Zealand White rabbits was performed to evaluate 50 µg of SARS-CoV-2 rS (BV2373 construct) with and without 50 µg Matrix-M adjuvant. Immunization of rabbits up to 4 times with full human doses of SARS- CoV-2 rS, with or without 50 µg Matrix-M adjuvant, was well tolerated and had no effects on mortality, cageside observations, body weight, food consumption, or physical examination

findings. There were no test article-related gross or histopathologic findings based on an examination of all body systems, including the myocardium and pericardium, aside from subacute inflammation at the injection sites, which was deemed a typical response to immunization. Findings from this study are considered relevant to the new vaccine constructs as the only significant changes are to the antigen and the rest of the vaccine constructs are produced using consistent manufacturing processes (MHRA 2021).

A GLP-compliant developmental and reproductive toxicity (DART) 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 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. The clinical development program for Novavax's SARS-CoV-2 rS with Matrix-M adjuvant comprises 4 ongoing clinical studies: a Phase ½ 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 subjects 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

Study 2019nCoV-101 was the first clinical study initiated with SARS-CoV-2 rS nanoparticle vaccine. This 2-part, randomized, observer-blinded, placebo-controlled, Phase ½ trial now has final results for study Part 1 and through Day 217 for study Part 2.

Study 2019nCoV-101 – Part 1 (Phase 1) was designed to evaluate the immunogenicity and safety of 5 and 25 µg SARSCoV-2 rS nanoparticle -vaccine with or without 50 µg Matrix-M adjuvant in 134 healthy participants ≥ 18 to ≤ 59 years of age. Results for the Phase 1 portion of the trial showed that SARS-CoV-2 rS with Matrix-M adjuvant was well tolerated and elicited robust immune responses. There were no serious adverse events (SAEs) or adverse events of special interest (AESIs) reported. Reactogenicity was mainly mild in severity and of short duration (mean ≤ 2 days), with second vaccinations inducing greater local and systemic reactogenicity. The adjuvant significantly enhanced immune responses (anti-S IgG, hACE2 receptor binding

inhibition antibody, and neutralizing antibody) and was antigen dose-sparing. The vaccine also induced antigen specific-T cells with a largely type 1 T helper (Th1) phenotype. An interim analysis performed at Day 35 using COVID-19 convalescent sera found the 2-dose 5 µg SARS-CoV-2 rS/Matrix-M adjuvant induced mean anti-S IgG and neutralizing antibody responses that exceeded the mean responses in convalescent sera from COVID-19 patients with clinically significant illnesses.

Study 2019nCoV-101 – Part 2 (Phase 2) was designed to evaluate the immunogenicity, safety, and preliminary efficacy of 5 and 25 µg SARS-CoV-2 rS nanoparticle vaccine with 50 µg Matrix-M adjuvant in up to 1,500 healthy adults ≥ 18 to ≤ 84 years of age with more comorbidities than the participant population in Part 1 of the study. Study vaccinations comprised up to 3 intramuscular (IM) injections (Day 1 and Day 21 [priming doses] and Day 189 [booster – active or placebo]). A subset of participants received a fourth injection at Day 357. A 217-day safety and immunogenicity analysis was conducted on 1,283 participants. This analysis comprised 700 participants aged 18 to 59 years (the same age range of Part 1 of the study) and 583 participants aged 60 to 84 years. Overall, local and systemic reactogenicity data from this analysis were consistent with the reactogenicity data in Part 1 of the study, with no safety concerns between the younger and older age cohorts. Both the 5 and 25 µg doses of SARS-CoV-2 rS with Matrix-M adjuvant were well tolerated with few participants (9; 0.7%) having SAEs. Regarding immunogenicity, robust responses were observed in both younger and older adults in the 2-dose 5 µg SARS-CoV-2 rS/Matrix-M adjuvant arm. While an attenuation of immune responses (approximately 2-fold lower SARS-CoV-2 wild-type neutralizing antibody activity in older participants) was observed when stratified by age group (18 to 59 years, inclusive and 60 to 84 years, inclusive), geometric mean fold increases in neutralizing antibodies were still increased > 95-fold compared to baseline.

Study 2019nCoV-501 is a Phase 2a/b, 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 (NVX-CoV2373), administered 21 days apart on Days 0 and 21 as a coformulation, in 4,164 healthy HIV-negative participants 18 to 84 years of age and 244 medically stable HIV-positive participants 18 to 64 years of age conducted in South Africa. Participants were randomized equally between vaccine and placebo for the initial vaccination period. Following the initial vaccination period, participants in the active treatment arm received one booster injection and one placebo injection 21 days apart, and the placebo group crossed over to receive active vaccine (2 injections 21 days apart). An analysis of the primary efficacy endpoint, which included both immunogenicity and safety data, was performed. A total of 147 polymerase chain reaction (PCR)-confirmed symptomatic mild, moderate, or severe COVID-19 cases were accrued for the complete analysis of the primary efficacy endpoint, with 51 (3.62%) cases for NVX-CoV2373 vs 96 (7.05%) cases for placebo. The resultant vaccine efficacy of NVX-CoV2373 in prevention of symptomatic mild, moderate, or severe COVID-19 in adult participants, seronegative (to SARS-CoV-2) at baseline, was 48.6% (95% confidence interval [CI]: 28.4, 63.1), meeting the success criterion of a lower bound CI > 0. In HIV-negative and HIV-positive participants, the resultant vaccine efficacy was 55.4% (95% CI: 35.9, 68.9) and -35.4% (95% CI: -236.9, 45.6). Forty-one (93.2%) of 44 participants with a primary endpoint had whole genome sequence data available (samples from 3 cases in the placebo group could not be sequenced), and 38 (92.7%) of 41 were identified as the B.1.351 (Beta) variant, resulting in a

post-hoc vaccine efficacy of NVX-CoV2373 in prevention of symptomatic mild, moderate, or severe COVID-19 in all and HIV-negative adult participants, seronegative (to SARS-CoV-2) at baseline, of 43.0% (95% CI: -9.8, 70.4) and 51.0% (95% CI: -0.6, 76.1), respectively, for the B.1.351 (Beta) variant. NVX-CoV2373 induced robust immune responses (anti-S IgG and neutralizing antibody) in both HIV-negative and HIV-positive participants vs placebo. In baseline seronegative participants, immune responses were approximately 2-fold lower in HIV-positive participants vs HIV-negative participants. NVX-CoV2373 was well tolerated in both HIV-negative and HIV-positive participants, with similar frequencies of severe adverse events (AEs), SAEs, medically attended adverse events (MAAEs), and AESIs compared to placebo. Solicited local and systemic reactogenicity in all participants were higher for NVX-CoV2373 than placebo, but the majority of events were classified as grade 1. Pain and tenderness were the most frequently reported local AEs after each vaccination, with relatively short median durations (2.0 days for NVX-CoV2373 and 1.0 day for placebo). Headache, fatigue, and muscle pain were the most frequently reported systemic AEs after each vaccination, with relatively short median durations (2.0 days for NVX-CoV2373 and placebo).

Study 2019nCoV-302 is 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 MatrixM- 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 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 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), which were 1.3-fold (anti-S IgG) and 1.4-fold (neutralizing antibody) 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 SAEs, MAAEs, and 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 subjects 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.

2.1.4 Benefit:Risk Assessment

Novavax has collected safety, efficacy, and immunogenicity data from approximately 50,000 participants across 5 clinical trials, including 2 independent Phase 3 trials in the US/Mexico (Study 2019nCoV-301) and the UK (Study 2019nCoV-302). The data from these trials, along with supporting preclinical studies, indicate that the known and potential benefits of the vaccine outweigh its known and potential risks.

Myocarditis or pericarditis has been reported following vaccination with NVX-CoV2373 in clinical trials, and it is possible that these reports represent vaccine-associated adverse events similar to those associated with 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 require 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 CDC has published clinical considerations for myocarditis and pericarditis after receipt of mRNA COVID-19 vaccines among adolescents and young adults [CDC 2021] which makes specific recommendations for the management of such cases. A surveillance and management plan for suspected myocarditis and/or pericarditis cases based on CDC and AHA recommendations [CDC 2021, Law 2021, Gargano 2021] has been implemented in the clinical development plan of NVX-CoV2373.

Study Rationale

Novavax, Inc. has developed a recombinant vaccine adjuvanted with the saponin-based Matrix-M adjuvant for the prevention of disease caused by SARS-CoV-2 (NVX-CoV2373). Both nonclinical and clinical data to date support continued clinical development of SARS-CoV-

2 recombinant spike protein nanoparticle vaccines (SARS-CoV-2 rS) combined with Matrix-M adjuvant as potential vaccines against SARS-CoV-2.

The purpose of this study is to compare the immunogenicity and safety of 3 different lots of NVX-CoV2373 in previously vaccinated adult participants 18 to 49 years of age, inclusive. Data from the study are intended to support the overall manufacturing data submitted as part of the Biological License Application in the United States and as part of other Regulatory submissions in other countries.

3 OBJECTIVES AND ENDPOINTS

The purpose of this study is to compare the immunogenicity and safety of 3 different lots of NVX-CoV2373 in previously vaccinated adult participants 18 to 49 years of age, inclusive.

An overview of all study objectives and endpoints is provided in Table 2.

Table 2 Study 2019nCoV-307 Objectives and Endpoints

	Objectives	Endpoints
Primary	To demonstrate the equivalence of 3 different vaccine lots based on IgG responses.	IgG geometric mean ELISA unit (GMEU) concentrations (ie, GMEU/mL) to the SARS-CoV-2 spike protein at Day 29 in each treatment arm; equivalence will be demonstrated if the 95% confidence intervals [CIs] of GMEU concentrations for all pairs of lots are within the pre-specified equivalence range of 0.67 to 1.5 GMEU/mL.
Secondary	To characterize the IgG antibody responses to 3 different lots of NVX-CoV2373.	Proportion of participants in each treatment arm who achieve seroconversion (≥ 4-fold increase from baseline) in IgG concentrations to the SARS-CoV-2 spike protein at Day 29.
	To characterize the neutralizing antibody responses to 3 different lots of NVX-CoV2373.	• MN_{50} geometric mean titers to the SARS-CoV-2 spike protein at Day 29 in each treatment arm. • Proportion of participants in each treatment arm who achieve seroconversion (≥ 4-fold increase from baseline) in MN_{50} titers to the SARS-CoV-2 spike protein at Day 29.
	To characterize antibody responses in a human angiotensin-converting enzyme 2 (hACE2) receptor binding inhibition assay to the SARS-CoV-2 spike protein in participants vaccinated with 3 different lots of NVX-CoV2373.	• hACE2 inhibition assay titers (geometric mean titer [GMTs]) at Day 29 in each treatment arm • Proportion of participants in each treatment arm who achieve seroconversion (≥ 4-fold increase from baseline) in hACE2 titers concentrations to the SARS-CoV-2 spike protein at Day 29.

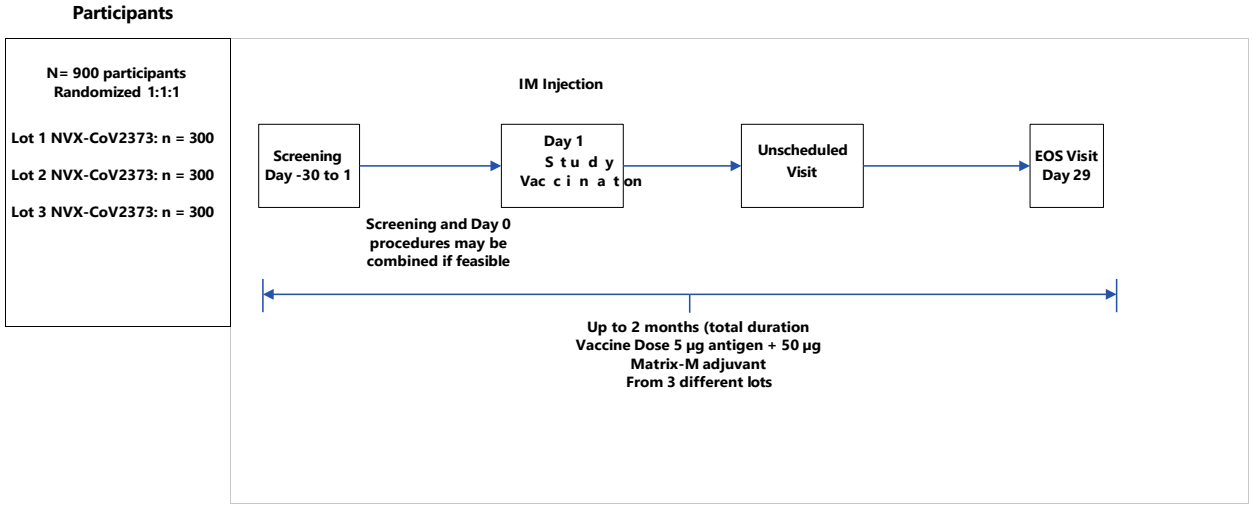
Table 2 Study 2019nCoV-307 Objectives and Endpoints

	Objectives	Endpoints
	To compare the overall safety of 3 different lots of NVX-CoV2373.	• Incidence, duration, severity, and relationship of MAAEs and AESIs (including myocarditis and/or pericarditis) through Day 29 (ie, 28 days after vaccine dose). • Incidence and relationship of SAEs throughout the study.
Exploratory	To utilize additional assays (current or to be developed) to best characterize the immune response for future vaccine development needs.	Additional endpoints to compare immune responses may be developed based on the assays used.

4 STUDY PLAN

4.1 Study Schematic

Figure 1 Flow Diagram for 2019nCoV-307



Abbreviations: EOS = end of study

4.2 Study Design

This is a randomized, Phase 3 study comparing the immunogenicity and safety of 3 different lots of NVX-CoV2373. The study will enroll approximately 900 previously vaccinated adults 18 to 49 years of age, inclusive.

Participants will be screened at baseline with the goal of enrolling approximately 900 previously vaccinated participants. Participants will be randomized 1:1:1 to receive 1 dose of the vaccine from 1 of 3 different lots, given on Day 1, at a dose level of 5 µg of antigen with 50 µg of Matrix-M adjuvant.

All participants will remain on study for immunogenicity and safety data collection through 28 days following the vaccination.

4.3 Design Rationale

Novavax, Inc. has developed a recombinant vaccine adjuvanted with the saponin-based Matrix-M adjuvant for the prevention of disease caused by SARS-CoV-2 (NVX-CoV2373).

The purpose of this study is to compare the consistency of immunogenicity and safety of the 3 different lots of NVX-CoV2373 in previously vaccinated adult participants 18 to 49 years of age. Data from the study are intended to support the overall manufacturing consistency data submitted as part of regulatory submissions in the US and elsewhere, as needed.

5 POPULATION

5.1 Recruitment

Approximately 1200 potential participants will be screened in order to meet the goal of 900 randomly assigned participants, who will be further divided into 3 groups of 300 participants each.

5.2 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 one or more eligibility criteria or who has withdrawn consent prior to treatment assignment. Screen failures may not be rescreened.

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

5.3 Inclusion Criteria

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

1. Adults 18 to 49 years of age, inclusive, at screening.
2. Willing and able to give informed consent 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 at least 12 consecutive months]) must agree to be heterosexually inactive from at least 28 days prior to enrollment and through the end of study (EOS) visit OR agree to consistently use a medically acceptable method of contraception from at least 28 days prior to enrollment and through the EOS visit.
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 study vaccination.
5. Agree 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. Documented receipt of either 2 or 3 doses of the investigational Novavax vaccine with Matrix-M adjuvant (NVX-CoV2373); OR documented receipt of a full course of an FDA-authorized/approved COVID-19 vaccine with or without a booster vaccine injection after primary series; OR documented receipt of a full course of heterologous COVID-19 vaccines mentioned above. The most recent dose must have been administered at least 6 months prior to study vaccination.

5.4 Exclusion Criteria

Participants meeting any of the following criteria will be excluded from the study.

1. History of laboratory-confirmed (by polymerase chain reaction [PCR] or rapid antigen test) COVID-19 infection ≤ 4 months prior to randomization.
2. Current participation in research involving receipt of an investigational product (drug/biologic/device).
3. Any known allergies or history of anaphylaxis to the active substance or any of the other ingredients contained in the investigational product.
4. Any autoimmune or immunodeficiency disease/condition (iatrogenic or congenital) or therapy that causes clinically significant immunosuppression.
5. Received any vaccine ≤ 90 days prior to study vaccination, except for influenza vaccine which may be received > 4 days prior to study vaccine, or rabies vaccine which may be received at any time if medically indicated.
6. 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.
7. Active cancer (malignancy) on chemotherapy that is judged to cause significant immunocompromise within 1 year prior to first study vaccination (with the exception of malignancy cured via excision, at the discretion of the investigator).
8. Participants who are breastfeeding, pregnant, or who plan to become pregnant prior to the EOS visit.
9. Suspected or known history of alcohol abuse or drug addiction within 3 months prior to the study vaccine dose that, in the opinion of the investigator, might interfere with protocol compliance.
10. 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 trial vaccine or interpretation of study results (including neurologic or psychiatric conditions likely to impair the quality of safety reporting).
11. 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).
12. Participants with a history of myocarditis or pericarditis.

6 STUDY CONDUCT

This is a Phase 3, randomized, study comparing the immunogenicity and safety of different lots of NVX-CoV2373. In this study, approximately 900 previously vaccinated adults 18 to 49 years of age will receive 1 dose of NVX-CoV2373 from 3 different lots, given on Day 1.

Following vaccination, all participants will remain on study for immunogenicity and safety data collection through Day 29 (EoS). Scheduled study visits will occur for Screening, Day 1, and Day 29.

6.1 Study Procedures by Visit

6.1.1 Screening Period

The following activities will occur at the Screening Visit. The Screening Visit can be and is expected to be combined with the Day 1 Visit.

- Informed consent
- Medical history, including prior and concurrent medical conditions and significant surgical procedures.
- Inclusion and exclusion criteria
- Demographics including age, sex, race, and ethnicity.
- Prior and concomitant medications, including recent (≤ 90 days) and current medications and vaccinations, are to be reviewed to ensure eligibility criteria are fulfilled. Concomitant medications include prescription and OTC (including vaccines) medications taken by the participant during the study. Do not record herbals, vitamins, and supplements.
- Vital sign measurements including respiratory rate, blood pressure, pulse rate, and temperature (oral or via forehead/ear reader). Urine pregnancy test in women of childbearing potential. A positive test will result in screen failure.
- Physical examination at screening to include height and weight, head nose ears and throat (HEENT), neck, lungs, heart, cardiovascular, abdomen, and musculoskeletal system/extremities to allow for study vaccination.
- Recording of SAEs.

6.1.2 Vaccine Administration Period (Day 1)

The following activities will occur at the Day 1 visit.

- Inclusion and exclusion criteria
- Prior/concomitant medications
- Vital sign measurements, including respiratory rate, blood pressure, pulse rate, and temperature (oral or via forehead/ear reader). Temperature will be taken prior to vaccination to ensure participant has no evidence of fever.
- Urine pregnancy test in women of childbearing potential. A positive test will result in disqualification.
- Baseline ECG
- Physical examination – symptom directed (targeted) if Screening and Day 1 are not combined into a single visit

- Nasal swab at clinic for SARS-CoV-2 (PCR)—anterior nares
- Blood sampling for SARS-CoV-2 (ELISA for anti-S protein serology, MN_{50} assay, and hACE2 receptor-binding inhibition assay)
- Randomization
- Vaccination
- Recording of SAEs, MAAEs, and AESIs (including potential immune-mediated medical conditions [PIMMCs] and myocarditis or pericarditis). See Table 4 for symptoms of myocarditis or pericarditis and Section 8.2.3.6 for instructions for follow-up.
- 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 reactions.

6.1.3 Unscheduled Visit

An Unscheduled Visit may be conducted by study personnel for safety follow-up for any participant experiencing a general medical issue while on study. During this visit, the following procedures will be performed:

- Prior/concomitant medications
- Vital sign measurements including respiratory rate, blood pressure, pulse rate, and temperature (oral or via forehead/ear reader).
- Physical examination – symptom directed (targeted)
- Recording of SAEs, MAAEs, and AESIs (including PIMMCs, myocarditis or pericarditis). See Table 4 for symptoms of myocarditis or pericarditis and Section 8.2.3.6 for instructions for follow-up.

NOTE: 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.

6.1.4 EOS (Day 29)

The following activities will be performed at the EOS Visit. EOS assessments will be conducted via an on-site visit.

- Prior/concomitant medications
- Vital sign measurements including respiratory rate, blood pressure, pulse rate, and temperature (oral or via forehead/ear reader).
- Physical examination – symptom directed (targeted)
- Blood sampling for SARS-CoV-2 (ELISA for anti-S protein serology, MN_{50} assay, and hACE2 receptor-binding inhibition assay)
- Recording of SAEs, MAAEs, and AESIs (including PIMMCs, myocarditis or pericarditis). See Table 4 for symptoms of myocarditis or pericarditis and Section 8.2.3.6 for instructions for follow-up.

6.2 Discontinuation or Withdrawal

6.2.1 Withdrawal from Study

Participants are free to withdraw from the study at any time upon request. Participant 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 but are encouraged to remain in the study for safety follow-up. In such cases, where only safety is being evaluated, participant contact may be managed via telemedicine contact (eg, telephone, web chat, video, FaceTime).

6.2.1.1 Replacement of Participants

Participants who withdraw, are withdrawn or terminated from this study, or are lost to follow up after signing the informed consent form (ICF) but prior to study vaccination may be replaced. Participants who receive study vaccine and subsequently withdraw, discontinue, are terminated from the study, or are lost to follow-up will not be replaced.

6.2.1.2 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 electronic case report form (eCRF). Data that would have been collected at subsequent visits will be considered missing.

6.3 Study Termination by Sponsor

Although the Sponsor has every intention of completing the study, it reserves 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). 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 (CSR).

7 STUDY INTERVENTIONS

Study vaccinations will comprise 1 IM injection of NVX-CoV2373 of 0.5 mL injection volume at a dose of 5 µg antigen (Table 3).

Table 3 Study Vaccinations

Vaccine	Age (years)	Baseline Serostatus	Number of doses	Number of participants	Dose (antigen/ Matrix-M adjuvant)
Lot 1 (Group 1)	18 to 49	Previously vaccinated	1	300	5 µg / 50 µg
Lot 2 (Group 2)	18 to 49	Previously vaccinated	1	300	5 µg / 50 µg
Lot 3 (Group 3)	18 to 49	Previously vaccinated	1	300	5 µg / 50 µg

7.1 Description of Products

7.1.1 NVX-CoV2373

7.1.1.1 Formulation, Storage, Preparation, and Handling

NVX-CoV2373 Prototype SARS-CoV-2 rS vaccine will be supplied as a solution for preparation for injection of SARS-CoV-2 rS at a concentration of 10 µg/mL and Matrix-M adjuvant at a concentration of 100 µg/mL.

NVX-CoV2373 should be stored at 2 to 8°C in a secured location. DO NOT FREEZE. The study site will maintain a temperature log to establish a record of compliance with storage conditions.

Further details on the trial vaccine can be found in the SARS-CoV-2 rS IB and a description of its preparation can be found in the Pharmacy Manual.

7.1.1.2 Packaging and Labeling

The Sponsor will provide adequate quantities and appropriate labelling of SARS-CoV-2 rS with Matrix-M adjuvant and Syneos Health will ensure distribution to the study sites from a designated depot. The clinical unit pharmacy or equivalent will prepare the clinical trial materials. Detailed instructions for the handling of trial vaccine vials will be provided in a separate Pharmacy Manual.

7.1.1.3 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 the vaccine should be administered according to standard practice by qualified study site personnel in a way to maintain overall blinding, as described in the Pharmacy Manual.

All participants will be administered 1 single IM injection of NVX-CoV2373 of 0.5 mL injection volume on Day 1.

7.1.1.3.1 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 4), pending review of cases by the Central Cardiac Adjudication Committee that will report the results of their adjudication to the Sponsor to recommend whether enrollment may be resumed.

7.1.2 Treatment Assignment and Bias Minimization

7.1.2.1 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 code with true treatment allocations will be held by Syneos Health during the study. Another randomization list (containing treatment) will be provided to clinical supplies.

7.1.2.2 Assessment and Verification of Compliance

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), if the full dose was administered, 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.

7.1.2.3 Blinding

This is an observer-blinded study. To maintain the blind, unblinded study site personnel will manage vaccine logistics, preparation, and 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 trial vaccine.

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

An IWRS will be responsible for the allocation of randomization numbers to individual participants. Randomization will take place at baseline after confirmation that the participant meets the inclusion/exclusion criteria. A copy of the randomization code with true treatment allocations will be held by Syneos Health during the study. Another randomization list (containing treatment) will be provided to clinical supplies.

7.2 Prior and Concomitant Therapies

Administration of medications, therapies, or vaccines will be recorded in the concomitant medication 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 from the time of signing the ICF 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 all COVID-19 vaccines prior to screening should be recorded in the Vaccine History eCRF. Site staff will record the date(s) and brand of the SARS-CoV-2 vaccine received.

7.2.1 Prohibited Therapies

The following therapies are prohibited within the specified timeframes of study conduct:

- Seasonal influenza vaccine may not be administered < 4 days before or < 7 days after the study vaccine.
- No other vaccine except rabies vaccine (if medically indicated) ≤ 90 days before randomization until EOS.
- No investigational product (drug/biologic/device) from time of randomization until after the last study visit.
- No immunoglobulins, monoclonal antibodies, blood products, or any therapy that causes clinically significant immunosuppression within 90 days of study vaccination until the EOS visit. Similarly, rabies immune globulin should be administered if medically indicated.

8 SAFETY ASSESSMENTS

The timing and frequency of all safety assessments are listed in the SOE (Table 1). Recording of unsolicited AEs will be conducted by electronic data capture (EDC). AESIs, including PIMMCs, myocarditis or pericarditis and AESIs specific to complications of potential disease enhancement for COVID-19 or those of specific interest potentially related to COVID-19 vaccines will also be monitored and are to be reported according to timelines specified for SAEs (see **APPENDIX 2** 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 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 exam, vital signs measurements) that are clinically significant in the medical and scientific judgment of the Investigator 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 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 an 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 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 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 he/she has reviewed the AE/SAE and has 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** – An AR is any AE caused by the investigational product.
- **Suspected adverse reaction (SAR)** – An SAR is any AE for which there is a reasonable possibility that the investigational product 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 drug 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.
- **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.
- Life-threatening: These events require an ER visit or hospitalization.

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.

8.2 Documenting Adverse Events

Reactogenicity reactions will be collected if they meet the criteria for a MAAE, SAE, or AESI.

At every study visit following Screening, participants will be asked a standard question to elicit 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).

Care will be taken not to introduce bias when detecting 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 disorders listed in **APPENDIX 2**.

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.

8.2.1.1 Assessment of Causality

There may be situations in which an SAE occurs 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.
- Re-challenge following second vaccination, if applicable.
- Medical history.
- Study treatment.
- Mechanism of action of study vaccine.
- Class effect (adjuvanted protein vaccines).
- Concomitant treatments in use.
- Withdrawal of study treatment.
- Lack of efficacy/worsening of existing condition.
- Possible vaccine enhancement of COVID-19.

8.2.2 Time Frame for Collection

AEs reported or observed during the study will be recorded on the AE page of the eCRF.

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

All AESIs and MAAEs 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, MAAEs, SAEs, cases of multisystem inflammatory syndrome, and hospitalized or fatal cases of COVID-19 following vaccination must be reported based on local regulatory reporting guidance for safety events.

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, he/she should promptly notify the Sponsor.

8.2.3 Classification of Events

8.2.3.1 Treatment-Emergent Adverse Event

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

8.2.3.2 Adverse Events of Special Interest

Participants will be assessed for diagnosis of an AESI at all study visits. AESIs include PIMMCs, myocarditis or pericarditis, AEs specific to COVID-19, or other potential AEs that may be determined at any time by regulatory authorities as additional information concerning COVID-19 is obtained. Listings of AESIs are presented in Appendix 2.

8.2.3.2.1 Myocarditis and/or Pericarditis (CDC Definition)

Participants reporting signs or symptoms of myocarditis or pericarditis (fatigue, acute chest pain, shortness of breath, etc.[see Table 4]) within 4 weeks after vaccination should be evaluated as soon as possible by a physician who should initiate a 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 5). A Central Cardiac Adjudication Committee has been established to adjudicate probable 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 relevant eCRF pages. Participants with confirmed myocarditis or pericarditis will be followed-up to document resolution of symptoms and/or abnormal test findings.

Table 4 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. 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.
3. 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.
4. Using either the original or the revised Lake Louise criteria [Ferreira 2018].
5. Based on the 2015 ESC Guidelines for the diagnosis and management of pericardial diseases [Adler 2015].
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 5 Management of Suspected 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.

8.2.3.2.2 Electrocardiograms

All participants will undergo a baseline ECG at Day 1 prior to study vaccine administration. Baseline ECGs will be read and interpreted by a Central Cardiac Adjudication Committee only as a comparison with new ECG(s) in the event that the participant experiences a cardiac event during the 28 days following vaccine administration that requires review by the Cardiac Adjudication Committee.

8.2.3.3 Medically Attended Adverse Events

MAAEs are defined as AEs with medically attended visits, including hospital, emergency room, urgent care clinic, or other visits to or from medical personnel for any reason. Routine study visits will not be considered. MAAEs will be reported from the time of study vaccination until Day 29.

8.2.3.4 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 a clinical study pregnancy form. To ensure participant safety, each pregnancy must be reported to Syneos Health within 24 hours of learning of its occurrence. Each 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 Syneos Health using the pregnancy reporting forms 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:

[redacted]

8.2.3.5 Overdose or Misuse

A drug overdose is defined as the accidental or intentional use of a drug or medicine or an administration error in an amount that is higher than is normally used. Every overdose must be reported to the CRO 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 eCRF AE page. Only overdoses associated with a clinical SAE needs to be reported as an SAE. The quantity and duration of 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 7.1.1.3). 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.

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 the appropriate CRO 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 AESIs related to COVID-19 are to be reported within these timelines. 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 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 the CRO 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 AESIs will also be recorded in the eCRF. The investigator is responsible for informing the Institutional Review Board (IRB) of the SAE as per local requirements.

Notification should be made within 24 hours using the dedicated fax line or email for the Syneos Health pharmacovigilance group:

Syneos Health Safety and Pharmacovigilance fax number: [redacted]

Syneos Health Safety and Pharmacovigilance email address: [redacted]

The report form should be attached to the email or fax; 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.

8.3.1.1 Safety Reporting to Sponsor

Syneos Health will forward the SAE/AESI and pregnancy reports to the Sponsor's safety representative(s) within 1 business day or 3 calendar days (whichever is earlier) of becoming aware of it.

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

Syneos Health will notify the Sponsor of any SAE and will perform follow-up activities with the concerned study site. Syneos Health will retain responsibility of expedited and periodic reporting according to national requirements. Procedure and timelines for safety reporting are provided in the Safety Management Plan as agreed by Syneos Health and the Sponsor. The Investigator must comply with any applicable study site-specific requirements related to the reporting of SAEs (particularly deaths and Suspected Unexpected Serious Adverse Reaction [SUSARs]) to the IRB that approved the study. Investigators should provide written documentation of IRB notification for each report to the CRO. In accordance with ICH GCP, Syneos Health will inform the investigators of findings that could adversely affect the safety of participant, impact the conduct of the study, or alter the IRB's approval/favorable opinion to continue the study, as assessed by the Sponsor. In particular and in line with respective regulations, the CRO will inform the investigators of SUSARs. The investigator should place copies of Safety Reports in the

Investigator Site File. National regulations with respect to Safety Report notifications to investigators will be taken into account. When specifically required by regulations and guidelines, the CRO will provide appropriate Safety Reports directly to the concerned lead IRB and will maintain records of these notifications. When direct reporting is not clearly defined by national or study site-specific regulations, the investigator will be responsible for promptly notifying the concerned IRB of any Safety Reports provided by the CRO and of filing copies of all related correspondence in the Investigator Site File.

8.3.1.3 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 questions an on-call physician can be reached 24 hours 7 days a week (24/7):

- Telephone: [redacted]

9 ANALYSIS

This section includes a description of the statistical strategy and considerations for the study. Further detailed specifications for the analysis of data from the study will be presented in a Statistical Analysis Plan.

9.1 Sample Size Rationale

The sample size and power are driven by the primary endpoint (ie, lot consistency in terms of immunogenicity measured by IgG response at Day 29). Based on IgG data from Novavax's study 2019nCoV-101 Part 2, previously vaccinated participants in the 18-49-year-old age group who received the SARS-CoV-2 rS vaccine, exhibited an 80% confidence upper bound of Day 29 IgG SD in $\log_{10}$ scale of 0.39. The immunogenic performance of the released lots should be approximately the same, ie, the lot-to-lot GMEU ratio should approximate 1.0. Under any manufacturing practices, between-lot variation exists and is considered normal. Assuming 10% variation (lot-to-lot GMEU ratio is 1.1), an evaluable sample size of 248 subjects for each lot in the per-protocol population will be required to achieve 97% power to demonstrate the lot-to-lot equivalence and provide the overall power of ~90% for all three lot-to-lot equivalence tests (Lot 1 vs. Lot 2, Lot 1 vs. Lot 3, and Lot 2 vs. Lot 3). Accounting for a ~5% dropout rate, a total enrollment sample size of 300 participants will provide 262 participants per lot.

The statistical success criterion for demonstrating the equivalence of each lot (Lot 1, Lot 2, and Lot 3) is based on the IgG response at Day 29. Equivalence will be demonstrated if the 95% CIs of GMEUs for all pairs of lots are within the pre-specified equivalence range of 0.67 to 1.5.

9.2 Analysis Sets

The following analysis sets are identified for analysis.

9.2.1 Randomized Participants Analysis Set

The Randomized Participants Analysis Set will include all participants who are randomized/enrolled, regardless of whether they actually received any study vaccine. The 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 a dose of study vaccine, regardless of protocol violations or missing data. Participants in the FAS will be analyzed according to the vaccine group as randomized. Immunogenicity summaries and associated statistical analyses will be based primarily on the PP Analysis Set and may also be analyzed in the FAS.

9.2.3 Safety Analysis Set

The Safety Analysis Set will include all participants who provide consent, are randomized/enrolled, and receive 1 dose of study vaccine. Participants in the Safety Analysis Set will be analyzed as actually treated. The Safety Analysis set will be used for all safety analyses.

9.2.4 Per-Protocol Analysis Set

The PP Analysis Set will include all participants who receive the study vaccine according to the protocol, have serology results for Day 1 and Day 29 available after the vaccination, and have no major protocol violations that are considered clinically relevant to impact immunogenicity response as determined by Novavax prior to database lock.

The analysis of the primary endpoint will be performed using the PP Analysis Set.

Within the PP Analysis Set there are 3 subsets defined: Anti-S Protein IgG Serology Subset, Neutralization Assay Subset, and the hACE2 Receptor-binding Inhibition Assay Subset.

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 prior to study vaccination will be included in this subset.

9.2.4.2 Neutralization Assay Subset

All participants in the PP Analysis Set who are tested for neutralization prior to study vaccination 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 ACE2 receptor-binding inhibition prior to study vaccination will be included in this subset.

9.3 Statistical Analyses

9.3.1 Background Analyses

9.3.1.1 Disposition and Protocol Compliance

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

The number (percentage) of participants in the Randomized Participants Analysis Set, FAS, Safety Analysis Set, and PP Analysis Set who have completed the study (from Day 1 through Day 29) will be summarized overall and by the study vaccine group.

The number (percentage) of participants in the Safety Analysis Set who discontinue the study prior to EOS and the reason for discontinuation (eg, AE, investigator decision, lost to follow-up, non-compliance) will be presented overall and by the study vaccine group. A listing of all participants discontinued from the study will be presented, including the reason for discontinuation and day of last study contact. Day of last study contact will be calculated as follows: date of study discontinuation minus date of Day 1 vaccination +1. A listing of all screened participants who failed the inclusion/exclusion criteria will also be provided.

The number (percentage) of participants in the Safety Analysis Set with major protocol deviations recorded throughout the study will be summarized by study vaccine group and protocol deviation category (Section 11.1.3). A listing of all participants with one or more major protocol deviations will also be provided and will include study vaccine group, study day

associated with the deviation relative to Day 1, protocol deviation category, and a description of the deviation as recorded by the site.

9.3.1.2 Demographics and Baseline Characteristics

Baseline demographic and background characteristics (eg, age, sex, ethnicity, race, height, weight, body mass index [BMI, derived], and ECG) will be summarized overall and by the study vaccine group for the FAS, Safety Analysis Set, and PP Analysis Set. 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 Medical Dictionary for Regulatory Activities (MedDRA) terms. Baseline medical history recorded at Screening will be summarized by the study vaccine group and by MedDRA System Organ Class/Preferred Term (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.

Participants will also be summarized by the study vaccine group and the name of previous COVID-19 vaccination. In addition, the time between first dose of previous COVID-19 vaccination and Day 1 vaccination dose may be summarized by the study vaccine group using descriptive statistics.

9.3.2 Immunogenicity Analyses

The immunogenicity analysis will be performed using the PP Analysis Set.

For the primary endpoint of IgG (GMEU/mL) to the SARS-CoV-2 spike protein in previously vaccinated participants 18 to 49 years of age, IgG GMEU, geometric mean fold rise ($GMFR_{Post/Pre}$), and SCR will be summarized overall and by study vaccine group.

IgG GMEU is calculated as the antilog of the mean of the log-transformed IgG GMEU at Days 1 and 29. $GMFR_{Post/Pre}$ is calculated as the ratio of post-vaccination IgG GMEU at Day 29 to pre-vaccination IgG GMEU at the baseline (Day 1).

Between-group ratio of IgG GMEUs (GMEUR) at Day 29 and the two-sided 95% CIs will be computed using analysis of covariance (ANCOVA), with the study vaccine group as the fixed effect and the ELISA unit at Day 1 (adjusted for intergroup variation in baseline [pre-vaccination] ELISA unit) as the covariate under two-sided type I error rate of 0.05. No type I error rate adjustments will be made. The mean difference of all lots paired comparisons with their corresponding CI limits will then be exponentiated to obtain IgG GMEUR and the corresponding 95% CIs.

As the 1st secondary endpoint of IgG GMEUs (EU/mL) to the SARS-CoV-2 spike protein, SCR (proportion of participants who achieve seroconversion ≥ 4-fold increase from baseline) in IgG GMEUs at Day 29 with corresponding two-sided exact binomial 95% CIs will be calculated using the Clopper-Pearson method. Two-sided 95% CIs of the difference in SCRs in IgG GMEU concentrations for all lots paired comparisons will be based on the Miettinen and Nurminen method.

For the 2nd secondary endpoints of neutralizing antibody response to 3 different lots of NVX-CoV2373 in previously vaccinated participants 18 to 49 years of age, MN_{50} GMT, $GMFR_{Post/Pre,}$ and SCR will be summarized overall and by the study vaccine group.

MN_{50} GMT is calculated as the antilog of the mean of the log-transformed MN_{50} titers at Days 1 and 29. GMFR is calculated as the ratio of post-vaccination MN_{50} GMTs at Day 29 to pre-vaccination MN_{50} GMTs at the baseline (Day 1).

Between-group ratio of MN_{50} GMTs (GMTR) at Day 29 and the two-sided 95% CIs will be computed using ANCOVA, with the study vaccine group as the fixed effect and the titer at Day 1 (adjusted for intergroup variation in baseline [pre-vaccination] titers) as the covariate under two-sided type I error rate of 0.05. No type I error rate adjustments will be made. The mean difference of all lots paired comparisons and comparisons of combined 3 lots with each lot with their corresponding CI limits will then be exponentiated to obtain MN_{50} GMTRs and the corresponding 95% CIs.

SCR (proportion of participants who achieve seroconversion ≥ 4-fold increase from baseline) in MN_{50} titers at Day 29 with corresponding 2-sided exact binomial 95% CIs will be calculated using the Clopper-Pearson method. Two-sided 95% CIs of the difference in SCRs in MN_{50} titers for all lots paired comparisons and comparisons of combined 3 lots with each lot will be based on the Miettinen and Nurminen method.

For the 3rd secondary endpoints of antibody responses in a hACE2 receptor-binding inhibition assay, hACE2 GMTs, $GMFR_{Post/Pre}$, and SCR will be summarized overall and by the study vaccine group (Lot 1, Lot 2, and Lot 3), and between-group hACE2 GMTR and difference in SCRs in hACE2 titers will be calculated using the same statistical methods applied for MN_{50} titers.

The same statistical methods applied for the analysis of $MN_{50,}$ IgG, and hACE2 may also be applied to characterize the immune response for future vaccine development needs as the exploratory endpoints.

9.3.3 Safety Analyses

The secondary endpoint, safety data include MAAEs and AESIs (predefined list) through Day 29 (ie, 28 days after vaccine dose) and SAEs throughout the study. All safety analyses will be descriptive and conducted using the Safety Analysis Set.

Unsolicited MAAEs through Day 29 including AESIs (predefined list), and SAEs throughout the study will be summarized overall and by the study vaccine group and by SOC and PT using MedDRA terms, as well as by severity and relationship to the study vaccine to present the number and percentage with its corresponding exact 95% CIs using Clopper-Pearson method. For multiple occurrences of an AE in the same participant, a participant will be counted only once within an SOC or a PT, using the most severe occurrence and closest reported relationship for the summarization by severity or relationship to the study vaccine, respectively. The duration of MAAEs and AESIs through Day 29 will also be summarized.

A by-participant listing of MAAEs and AESIs through Day 29 and SAEs throughout the study will also be provided.

9.3.3.1 -Prior and Concomitant Medications and Vaccinations

Prior and concomitant medications and vaccinations will be summarized overall and by study vaccine group and preferred drug name as coded using the WHO drug dictionary for all participants in the Safety Analysis Set. Multiple occurrences of medication usage for a participant will be counted only once within an anatomical therapeutic chemical (ATC) term and standardized medication name. A by-participant listing of treatment-emergent concomitant medications (including vaccines) will be presented.

9.3.3.2 Vital Sign Measurements

Vital sign measurements including temperature, respiratory rate, blood pressure, and pulse rate will be summarized as continuous variables. Descriptive statistics for vital signs will be presented by study vaccine group for all participants in the Safety Analysis Set, including means and SDs, median, minimum, and maximum. A by-participant listing of vital signs will be provided.

9.3.3.3 Physical Examinations

Physical examination at screening will include height and weight, HEENT, neck, lungs, heart, cardiovascular, abdomen, and musculoskeletal system/extremities to allow for study vaccination. Symptom-directed (targeted) physical examination will be performed at all other scheduled time points. Abnormal results will also be summarized as clinically significant or not clinically significant.

9.4 Interim Analyses

No interim analysis is planned.

9.5 Final Analysis

The final analysis will be performed when the complete data for IgG GMEUs, MN_{50} titers, hACE2 titers, and safety data throughout the study (from Day 1 through Day 29) are available.

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 HREC/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 permission for the storage of serum samples for future research purposes.

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:

1. 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.
2. 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 Health 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 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. The monitor will be blinded to study vaccine assignment. A separate unblinded study monitor will be responsible for drug accountability.

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 SOPs.

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, if 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 paper diary created for the study. These data collection tools are a validated EDC system that contains a system generated audit trail. Data required according to this protocol are recorded by study site personnel via data entry into the internet-based EDC software system or by study participant via the paper diary. 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 Health 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, and complete medical history and physical examination reports.

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.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study vaccine or per local regulation, whichever is longer. These documents should be retained for a longer period, however, if required by applicable regulatory requirements or by an agreement with the Sponsor. 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 Syneos Health 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 Syneos Health nor the study site is financially responsible for further treatment of the disease under study.

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15 APPENDICES

APPENDIX 1 PROTOCOL CHANGE HISTORY

Protocol Version 5.0, 20 July 2022 (revised from Version 4.0, 29 June 2022)

The following is a summary of changes made to the protocol.

Location of Change	Change/Modification in Version 5.0, 20 July 2022
Synopsis and Table 2: Secondary Endpoints	Deleted "key" from description of Secondary Objectives and Endpoints

Protocol Version 4.0, 29 June 2022 (revised from Version 3.0, 13 June 2022)

The following is a summary of changes made to the protocol.

Location of Change	Change/Modification in Version 4.0, 29 June 2022
Abbreviations	Added ECG to list of abbreviations.
Synopsis and Table 2: Primary Endpoint	Added "Equivalence will be demonstrated if the 95% CIs of GMEUs for all pairs of lots are within the pre-specified equivalence range of 0.67 to 1.5 GMEU/mL"
Section 7.1.1.3.1: Study Vaccination Pause Rules	Strengthened pause rule to read "Central Cardiac Adjudication Committee that will report the results of their adjudication to the Sponsor to recommend whether enrollment may be resumed".
Section 9.1 Sample Size Rationale	Added the following sentence to meet requirements of regulatory agency: "The statistical success criterion for demonstrating the equivalence of each lot (Lot 1, Lot 2, and Lot 3) is based on the IgG response at Day 29. Equivalence will be demonstrated if the 95% CIs of GMEUs for all pairs of lots are within the pre-specified equivalence range of 0.67 to 1.5."
Section 9.3.1.2: Demographics and Baseline Characteristics	Added ECG to list of assessments.
Section 9.3.3: Safety Analyses	Deleted ECG information that was added to Section 9.3.1.2.
Section 9.3.3.2 Vital Signs	Deleted "Vital signs will be summarized by study vaccine group and severity" to correct error.

Protocol Version 3.0, 13 June 2022 (revised from Version 2.0, 01 April 2022)

The following is a summary of the changes made to the protocol.

Location of Change	Change/Modification in Version 3.0, 10 June 2022
Title Page	Replaced Human Research Ethics Committee with Institutional Review Board as this study will be conducted in the United States
Synopsis, Study Rationale, Section 4.3	Clarified that the purpose of the study is to compare the consistency of immunogenicity and safety of 3 different lots of NVX-CoV2373
Synopsis	Removed Inclusion/Exclusion Criteria and Statistical Methods and Sample Size Calculation per new protocol template
Synopsis, Table 3	Added Group numbers to Treatment Group table for clarity
Synopsis, Key Secondary Objectives and Corresponding Endpoints, Section 3 (Table 2)	Added myocarditis and/or pericarditis to the safety objective.
Synopsis, Number of Sites	Changed number of sites from up to 20 to approximately 30
Schedule of Events, Section 6.1.2	Added baseline ECG to Day 1 visit
Schedule of Events, Section 6.1.2, Section 6.1.3, Section 6.1.4	Added myocarditis or pericarditis to list of PIMMCs and added footnote 8 and text to account for surveillance for myocarditis and pericarditis
Section 2.1.3.1 Clinical Pharmacology and Safety	Updated to include updated clinical data from Study 2019nCoV-301
Section 2.1.4 Benefit-Risk Assessment	Added information about myocarditis and pericarditis
Section 5.3 Inclusion Criteria	Added "with or without a booster vaccine injection after primary series" to Inclusion Criterion 6
Section 5.4 Exclusion Criteria	Added rapid antigen test Exclusion Criterion 1 to expand history of laboratory confirmed COVID-19 criteria
Section 5.4 Exclusion Criteria	Added a new Exclusion Criterion: "Received any vaccine ≤ 90 days prior to study vaccination, except for influenza vaccine which may be received > 4 days prior to study vaccine, or rabies vaccine which may be received at any time if medically indicated"
Section 5.4 Exclusion Criteria	Added rabies immunoglobulin as an exception to Exclusion Criterion 6
Section 5.4 Exclusion Criteria	Added Exclusion Criterion 12: "Participants with a history of myocarditis or pericarditis"
Section 7.1.1.3.1	Added Study Vaccination Pause Rules for myocarditis and/or pericarditis
Section 7.5.1 Prohibited Therapies	Added restrictions for seasonal influenza vaccine and exception for rabies vaccine
Section 8 Safety Assessments	Added information about myocarditis and pericarditis and description of Central Cardiac Adjudication Committee and removed cross-reference to Appendix 3.

Location of Change	Change/Modification in Version 3.0, 10 June 2022
Section 8.2.3.2 Adverse Events of Special Interest	Added myocarditis and/or pericarditis as adverse events of special interest.
Section 8.2.3.2.1 Myocarditis and/or Pericarditis	Added a subsection on myocarditis and/or pericarditis
Section 8.2.3.2.2 Electrocardiograms	Added a subsection on electrocardiograms
Section 8.3 Reporting Adverse Events	Updated to include information about myocarditis and pericarditis
Section 9.2.4.1, Anti-S Protein IgG Serology Subset	Clarified that the Anti-S Protein Serology Subset is actually the Anti-S Protein IgG Serology Subset
Section 9.3.3 Safety Analyses	Added information about baseline ECG
Section 14 References	Added appropriate references based on changes
Appendix 3	Deleted Appendix 3 as FDA grading criteria will not be used in the study

Protocol Version 2.0, 01 April 2022 (revised from Version 1.1, 16 March 2022)

The following is a summary of the changes made to the protocol.

Location of Change	Change/Modification in Version 2.0, 01 April 2022
Schedule of Events,	Changed Day 29 visit to +4 days and removed -3 Revised footnotes 3 and 5 for clarity
Sections 6.1.1, 6.1.2, 6.1.3, 6.1.4	Deleted "pulse oximetry" from vital sign measurements Revised bullets to match footnotes
Section 7.5 Prior and Concomitant Medications	Clarified instructions for recording concomitant therapies.
Section 8 Safety Assessments	Deleted "solicited" since solicited AEs will not be assessed.
Section 8.2.3.4 Pregnancy	Deleted "If pregnancy occurs further vaccination will be discontinued." Deleted "The health status of the child may be followed through 12 months of age."
Section 8.2.3.5 Overdose or Misuse	Deleted reference to physical examination being performed at the unscheduled visit.
Section 9.3.1.2 Demographics and Baseline Characteristics	Added information about summarizing by study vaccine group, name of previous vaccine, and timing between previous vaccine and Day 1 vaccine.
Section 9.3.3 Safety Analysis	Updated description of safety analysis.

Section 9.3.3.2 Vital Sign Measurements	Added information about summarizing vital sign information.
Appendix 3	Added vital sign table because vital signs will be analyzed by severity.

Location of Change	**Change/Modification in Version 1.1, 16 March 2022**
Schedule of Events, Section 6.1.2	Added: On vaccination days, 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 reactions.

APPENDIX 2 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 PIMMC listed below (Table 6). 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 6 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, myeloradiculomyelitis), cranial nerve disorders including paralyses/paresis (eg, Bell's palsy), 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 chronic arthritis (including Still's disease), mixed connective tissue disorder, polymyalgia rheumatic, polymyositis, psoriatic arthropathy, relapsing polychondritis, rheumatoid arthritis, scleroderma (including diffuse systemic form and CREST syndrome), spondyloarthritis (including ankylosing spondylitis, reactive arthritis [Reiter's Syndrome] and undifferentiated spondyloarthritis), systemic lupus erythematosus, systemic sclerosis, Sjogren's syndrome.
Vasculitis	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], necrotizing vasculitis and ANCA-positive vasculitis [type unspecified], Henoch-Schonlein purpura, Behcet's syndrome, leukocytoclastic vasculitis).
Gastrointestinal Disorders:	Crohn's disease, celiac disease, ulcerative colitis, ulcerative proctitis.
Hepatic Disorders:	Autoimmune hepatitis, autoimmune cholangitis, primary sclerosing cholangitis, primary biliary cirrhosis.
Renal Disorders:	Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis).
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,

Table 6 Potential Immune-Mediated Medical Conditions

Categories	Diagnoses (as MedDRA Preferred Terms)
	pemphigoid and dermatitis herpetiformis), cutaneous lupus erythematosus, morphoea, lichen planus, Stevens-Johnson syndrome, Sweet's syndrome.
Hematologic Disorders:	Autoimmune hemolytic anemia, autoimmune thrombocytopenia, antiphospholipid syndrome, thrombocytopenia.
Metabolic Disorders:	Autoimmune thyroiditis, Grave's or Basedow's disease, new onset Hashimoto thyroiditis[a], 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.

DaSilva 2013

AEs specific to COVID-19 are listed below (Table 7). The list is not intended to be exhaustive, nor does it exclude the possibility that other diagnoses may be AESI.

Table 7 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.
Coagulopathy	Deep vein thrombosis, myocardial infarction, stroke.
Renal Disorders:	Acute kidney injury.
Hematologic Disorder	Thrombocytopenia, septic shock-like syndrome.
Inflammatory Disorders:	Cytokine Release Syndrome related to COVID-19 infection[2], 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 related to COVID-19 infection is a disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath (DAIDS 2017).