A Phase 3 Study to Evaluate the Immunogenicity and Safety of Novavax COVID-19 Vaccine(s) as Second or Subsequent Boosters After mRNA Vaccines in Individuals 18 to 49 Years of Age

Investigational Product(s)	NVX-CoV2373 and updated Novavax vaccine based on recent variant(s)
Protocol Number	2019nCoV-312
Clinical Trial Registry Identifiers	NCT05875701
Version Number	2.1
Version Date	26 March 2025
Amendment	1.1
Sponsor	Novavax, Inc. 21 Firstfield Road Gaithersburg, MD 20878 United States

Statement of Compliance

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

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

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

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

Sponsor's Approval

Title	A Phase 3 Study to Evaluate the Immunogenicity and Safety of Novavax COVID-19 Vaccine(s) as Second or Subsequent Boosters After mRNA Vaccines in Individuals 18 to 49 Years of Age
Protocol Number	2019nCoV-312
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The design of this study as outlined by this protocol has been reviewed and approved by the Sponsor's responsible personnel as indicated in the signature table below.

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

Investigator's Agreement

I have read the protocol, appendices, and accessory materials related to Study 2019nCoV-312 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 all 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**

Table of Contents

List of Tables

List of Figures

List of Appendices

List of Abbreviations

Abbreviation	Definition
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
GMEUR	Between-group ratio of IgG GMEUs
GMFR	Geometric mean fold rise
GMT	Geometric mean titer
GMTR	Between-group ratio of Nab GMTs
GP	Glycoprotein
hACE2	Human angiotensin-converting enzyme 2
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
IND	Investigational New Drug

Abbreviation	Definition
IRB	Institutional Review Board
MAAE	Medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East Respiratory Syndrome
MHC	Major histocompatibility complex
Nab	Neutralizing antibody
OTC	Over-the-counter
PCR	Polymerase chain reaction
PIMMC	Potential immune-mediated medical conditions
PP	Per-Protocol
PT	Preferred term
RNA	Ribonucleic acid
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
Sf9	Spodoptera frugiperda
SII	Serum Institute of India
SOC	System organ class
SOE	Schedule of Events
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
US	United States
WHO	World Health Organization

1 Synopsis

Title	A phase 3 study to evaluate the immunogenicity and safety of Novavax COVID-19 vaccine(s) as second or subsequent booster after mRNA vaccines in individuals 18 to 49 years of age
Short Title	Phase 3 study of Novavax vaccine(s) as booster dose after mRNA vaccines
Phase	Phase 3
Study Design	This is an open-label Phase 3 study evaluating the immunogenicity and safety of Novavax vaccine(s) with Matrix-M™ adjuvant (ancestral strain NVX-CoV2373 and an alternative strain and/or multivalent Novavax vaccine) as booster doses following a series of primary and booster doses of authorized/approved mRNA vaccines followed by a single booster dose of NVX-CoV2373 in the Novavax 2019nCoV-307 study (Study 307). This study will enroll up to 300 adult participants who previously participated in Study 307. Approximately 100-150 participants will receive 1 dose of ancestral strain NVX-CoV2373 vaccine, given on Day 1, at a dose level of 5 µg of ancestral strain antigen with 50 µg of Matrix-M adjuvant. Subsequently, another 100-150 participants may be enrolled to receive 1 dose of an updated Novavax vaccine based on recent variant(s) at a dose level of 5 µg total antigen with 50 µg of Matrix-M adjuvant. All participants will remain on study for assessment of immunogenicity at Day 29 and safety data collection through 6 months (Day 181) following the vaccination.
Target Population	Medically stable male and non-pregnant female prior participants who received their first booster of NVX-CoV2373 in Study 307 following prior priming and booster doses with mRNA vaccines.
Number of Participants	Total number of participants planned: Approximately 200 - 300; with 100 – 150 to receive a single dose of NVX-CoV2373 ancestral strain COVID-19 vaccine. 100-150 additional participants may be enrolled to receive a single dose of an updated Novavax COVID-19 vaccine based on recent variant(s).
Length of Participation	On study (including screening and follow-up): up to 7 months
Intervention	Ancestral strain SARS-CoV-2 rS vaccine is supplied as a suspension for injection, at a concentration of 10 µg rS antigen and 100 µg Matrix M adjuvant per mL. If introduced to the study, the updated variant Novavax vaccine will be supplied and prepared as described in the Pharmacy Manual. The regimen for any final preparations will comprise 1 intramuscular (IM) injection (Day 1) of 0.5 mL injection volume with a total dose of 5 µg recombinant rS antigen with 50 µg Matrix M adjuvant. Vaccine will be administered as an open-label material.
Primary Objective and Primary Endpoint	Hypothesis: Neutralizing antibody (Nab) responses following 1 booster dose of Novavax vaccine will be non-inferior to the increases observed in participants who received their first booster of Novavax vaccine in Study 307 following prior priming and booster doses with mRNA vaccines. Objective: To characterize the Nab responses (geometric mean titers [GMTs]) to ancestral strain Novavax vaccine administered as a second (or subsequent) booster after licensed mRNA vaccines and a first ancestral strain Novavax vaccine booster. Endpoints: • Nab GMTs to the ancestral strain SARS-CoV-2 at Day 29. Non-inferiority will be demonstrated if the lower-bound (LB) of the 95% confidence

	intervals (CIs) for the ratio of Nab GMT at Day 29 between the two booster periods is > 0.67. • If non-inferiority is demonstrated, results will be tested for superiority, defined as the LB of 95% CIs for the ratio of Nab GMT at Day 29 > 1.0.
Secondary Objective(s) and Corresponding Endpoint(s)	Objective: To further characterize the Nab responses (seroconversion rate [SCR]) to ancestral strain Novavax vaccine administered as a second (or subsequent) booster after licensed mRNA vaccines and a first ancestral strain Novavax vaccine booster. Endpoint: • Proportion of participants who achieve seroconversion (≥ 4-fold increase from baseline) in neutralization antibody titers to the SARS-CoV-2 at Day 29 compared with results of the same measurements in participants who received their first ancestral strain Novavax vaccine booster after mRNA vaccination in Study 307 in the same participants. Non-inferiority will be demonstrated if the LB of the 95% exact CIs for the difference of SCRs in Nab titers is higher than –10% Objective: To demonstrate the noninferior immunogenicity of Novavax vaccine as a second (or subsequent) booster vs as a first booster of ancestral strain Novavax vaccine following mRNA vaccines. Endpoint: • Immunoglobulin G (IgG) geometric mean enzyme-linked immunoassay (ELISA) unit concentrations (GMEU/mL) to the SARS-CoV-2 ancestral strain spike protein at Day 29; non-inferiority will be demonstrated if the LB of the 95% CIs for the ratio of IgG GMEU at Day 29 between the two booster periods is > 0.67. • If non-inferiority is demonstrated, results will be tested for superiority, defined as a lower 95% CI of GMEU ratio > 1.0. • Proportion of participants who achieve seroconversion (≥ 4-fold increase from baseline) in IgG concentrations to the SARS-CoV-2 ancestral strain spike protein at Day 29 compared with results of the same measurements in participants who received their first ancestral strain Novavax vaccine booster after mRNA vaccination in Study 307. Non-inferiority will be demonstrated if the LB of the 95% exact CIs for the difference of SCRs in IgG ELISA unit is higher than –10%. Objective: To characterize the cross-reaction of neutralizing and IgG antibodies induced by the ancestral strain Novavax vaccine to more recent SARS-CoV-2 variants for which appropriate assays are available. Endpoint: • Post-booster neutralizing GMTs and IgG GMEUs compared with post-first booster results from Study 307. Objective: To further characterize antibody responses in a human angiotensin-converting enzyme 2 (hACE2) receptor binding inhibition assay to the SARS-CoV-2 ancestral strain spike protein using the same calculations and comparison group for neutralizing and IgG antibodies. (second arm) Endpoint: • Seroresponse data from Study 307 participants enrolled to the second treatment group of this study to receive an updated Novavax vaccine based on recent variant will be assayed using the same assays as described above. hACE2 antibodies post-updated booster will be compared to those post-ancestral strain boosters and will be analyzed

	in the same manner specifically to assess reactivity with the ancestral strain virus/spike protein and with recent variant virus/spike protein. Objective: To describe the overall safety of ancestral strain and updated (if administered) Novavax vaccine(s) administered as a second (or subsequent) booster following licensed mRNA vaccines and a first ancestral strain Novavax vaccine booster. Endpoints: • Incidence, duration, and severity of solicited adverse reactions in the 7 days following study vaccination. • 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 181 after the vaccine dose. • Incidence and relationship of serious adverse events (SAEs) through Day 181 after the vaccine dose. .
Exploratory Objective(s) and Corresponding Endpoint(s)	Objective: To utilize additional assays (current or to be developed) to best characterize the immune response for future vaccine development needs, including testing against emerging variants of SARS-CoV-2. Endpoint: Additional endpoints to evaluate immune responses may be developed based on the assays used.
Number of Sites	Up to 20 sites in the US
Study Duration	Estimated duration: 6 months (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]**	**8**	**29**	**Unscheduled Visit**	**61**	**91**	**121**	**151**	**181**
Window (days)	**--**	**–**	**+3**	**+ 4**	**--**	**± 7**	**± 15**	**± 15**	**± 15**	**+ 15**
Study Visit	**Screening**	**1**	**2**	**3**		**Phone Call**	**Phone Call**	**Phone Call**	**Phone Call**	**EOS Phone Call**
Informed consent	X									
Medical history[2]	X				X					
Inclusion/exclusion criteria[3]	X	X[4]								
Demographics	X									
Prior/concomitant medications[5]	X	X[4]	X	X	X	X	X	X	X	X
Vital sign measurements	X	X[4]			X					
Urine pregnancy test (WOCBP)	X	X[4]								
Physical examination[6]	X	X[4]			X[7]					
Baseline ECG		X[4]								
Nasal swab at clinic for SARS-CoV-2 (PCR) – anterior nares		X[4]								
Blood sample for anti-NP testing		X[4]		X						
Blood sampling for SARS-CoV-2 (ELISA for anti S-protein serology, neutralizing antibody titers, and hACE2 receptor-binding inhibition assay)		X[4]		X						
Vaccination		X[8]								
Reactogenicity and diary collection		X[8,9]	X[9]							
SAEs	X	X	X	X	X	X	X	X	X	X
All unsolicited AEs		X	X	X	X					
MAAEs and AESIs (including PIMMCs, myocarditis or pericarditis)		X[10]	X[10]	X[10]	X[10,11]	X[11]	X[11]	X[11]	X[11]	X[11]

Table 1 Schedule of Events

Study Day	**–30 to 1[1]**	**1[1]**	**8**	**29**	**Unscheduled Visit**	**61**	**91**	**121**	**151**	**181**
Window (days)	**--**	**–**	**+3**	**+ 4**	**--**	**± 7**	**± 15**	**± 15**	**± 15**	**+ 15**
Study Visit	**Screening**	**1**	**2**	**3**		**Phone Call**	**Phone Call**	**Phone Call**	**Phone Call**	**EOS Phone Call**
EOS form[12]										X

Abbreviations: AESI = adverse event(s) of special interest; eCRF = electonic case report form; EDC = electronic data capture; ELISA = enzyme-linked immunosorbent assay; EOS = end of study; hACE2 = human angiotensin-converting enzyme 2; MAAE = medically attended adverse event; 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 should be combined if feasible at any given study site.
2. Significant medical history should be recorded, focusing on ongoing medical conditions.
3. Specific exclusions to study vaccination will be assessed before vaccination. Waivers to enrolling participants with exclusions will not be given.
4. Performed prior to study vaccination.
5. Recent (≤ 90 days) and current medications, including non-COVID-19 vaccines, should be recorded in the concomitant medication electronic case report form (eCRF). All COVID-19 vaccines administered prior to Screening should be recorded in the vaccine history eCRF. Do not record herbals, vitamins, and/or supplements. All assessments should be performed prior to vaccination. After Day 29, record all COVID-19 vaccines and only record concomitant medications and other vaccines that may have caused or are used to treat an AE.
6. Examination at Screening to include height and weight; cervical and axillary lymph nodes, heart and any other symptom-directed (targeted) examination.
7 A targeted physical examination should be performed as needed.
8. 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.
9. Reactogenicity (solicited adverse events related to vaccination) will be recorded by participants via diary on Days 1-7. The diary will be collected from the participant at the Day 8 visit and will be used to populate reactogenicity data in EDC. Should any reactogenicity event extend beyond 7 days after vaccination (toxicity grade ≥1), then it will be recorded as an AE with the same start date as the reactogenicity event and followed to resolution.
10. All MAAEs and all AESIs (including potential immune-mediated medical conditions [PIMMCs] and myocarditis or pericarditis will be recorded. See Table 3 for symptoms of myocarditis or pericarditis and Table 4 for instructions for follow-up.
11. MAAEs attributed to study vaccine and all AESIs (including PIMMCs and myocarditis or pericarditis) will be recorded. See Table 3 for symptoms of myocarditis or pericarditis and Table 4 for instructions for follow-up.
12. 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 evaluate the immunogenicity and safety of Novavax COVID-19 vaccine(s) as second or subsequent booster after mRNA vaccines in individuals 18 to 49 years of age.

2.1.1 Description of NVX-CoV2373

NVX-CoV2373 is the ancestral strain 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 coadministered 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 and supportive clinical and nonclinical study summaries can be found in the SARS-CoV-2 rS Investigator's Brochure (IB) (Novavax 2022).

2.1.2 Supportive Nonclinical Data

Supportive nonclinical data are available through studies conducted using Novavax manufactured SARS-Co- 2 rS products. Pharmacological properties of the SII-produced vaccines used in this study are expected to be equivalent to those produced by Novavax. Nonclinical safety, immunogenicity, and protective efficacy have now been confirmed in Phase 3 clinical trials. Nonclinical data can be found in the Investigator's Brochure.

A good laboratory practice (GLP)-compliant developmental and reproductive toxicity study was completed in Sprague-Dawley rats. Females were immunized with placebo, 5 µg of SARS-CoV-2 rS antigen with 10 µg of Matrix-M adjuvant, or 10 µg of Matrix-M adjuvant alone. These doses were approximately 40-fold in excess of the human dose, on a weight-adjusted basis, in a 50 kg human female. Doses were given on pre-mating Days 1 and 15, and then, after mating, at gestational Days 7 and 15. Dams immunized with antigen plus adjuvant, but not adjuvant alone, had strong anti-S 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 clinical studies: a Phase 1-2 study of SARS-CoV-2 rS with or without Matrix-M adjuvant in healthy adult participants 18 to 59 years of age (Study 2019nCoV-101– Part 1) and SARS-CoV-2 rS with Matrix-M adjuvant in healthy adult participants 18 to 84 years of age (Study 2019nCoV-101 – Part 2); a Phase 2a/b study of SARS-CoV-2 rS with Matrix-M adjuvant in healthy adult participants 18 to 84 years of age living without human immunodeficiency virus (HIV) and medically stable adult participants 18 to 64 years of age living with HIV (Study 2019nCoV-501); and 2 Phase 3 studies in healthy and medically stable adult participants ≥ 18 years of age and adolescent participants 12 to < 18 years of age (Study 2019nCoV-301) and 18 to 84 years of age (Study 2019nCoV-302). Additionally, Study 2019nCoV-307 (Study 307), which looked at the effect of homologous and heterologous boosting with NVX-CoV2373 in adults ≥18 years of age, formed the basis for this study and its

enrollment population. Clinical data from Phase 1-2 trials and additional clinical data from Phase 3 trials can be found in the Investigator's Brochure.

2.1.3.1 Clinical Pharmacology and Safety

Study 2019nCoV-302 was a Phase 3, randomized (1:1), observer-blinded, placebo-controlled trial evaluating the efficacy, safety, and immunogenicity of 5 µg SARS-CoV-2 rS with 50 µg Matrix M- adjuvant, administered 21 days apart on Days 0 and 21 as a coformulation, in 15,139 healthy and medically stable (with comorbidities) participants 18 to 84 years of age conducted in the 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 [Nab]), which were 1.3-fold (anti-S IgG) and 1.4-fold (Nab) higher in the younger age cohort (18 to 64 years) than in the older age cohort (65 to 84 years), but seroconversion rates (SCRs) were at least 98% in both age cohorts. NVX-CoV2373 was well tolerated, with similar frequencies of 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 participants 12 to < 18 years of age conducted in the US. In adults, final analysis of the primary efficacy endpoint yielded a VE of 90.41% (95% CI: 83.81, 94.32) for all participants. In addition, NVX-CoV2373 induced robust immune responses and safety data reflected an acceptable safety profile. These data were

submitted to the FDA in support of a request for Emergency Use Authorization. Subsequently, safety and immunogenicity data following a booster dose of NVX-CoV2373 from this study supported Emergency Use Authorization of the vaccine as a booster dose.

Study 307 is a phase 3 study that compared the immunogenicity and safety of 3 lots of NVX-CoV2373 in adults to demonstrate the consistency of effect among the 3 manufacturing lots of drug product. We also explored the immunogenicity of heterologous and homologous boosting on Wuhan and Omicron strains of COVID-19. NVX-CoV2373 showed equivalent immunogenicity across manufacturing lots, as measured by IgG and NAb responses. No new safety signals were identified. NVX-CoV2373 was also immunogenic regardless of whether it was used as a first booster or later booster dose, and whether it followed earlier doses of NVX-CoV2373 or other authorized vaccines. Additionally, it displayed immunogenicity against all 3 tested variants of SARS-CoV-2 rS. Participants in Study 307 who received a primary series of an mRNA vaccine were invited to participate in this study.

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, 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.

2.2 Study Rationale

Novavax, Inc. has developed a recombinant spike protein 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 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 assess safety and immunogenicity of ancestral strain NVX-CoV2373 and, possibly, an updated Novavax vaccine based on recent variant(s), when used as a second booster dose in individuals who have previously received a primary vaccine series of licensed mRNA with or without a subsequent mRNA booster dose followed by one booster with ancestral strain NVX-CoV2373 vaccine in Study 307.

3 Objectives and Endpoints

The purpose of this study is to evaluate the immunogenicity and safety of Novavax COVID-19 vaccine(s) as second or subsequent booster after mRNA vaccines in individuals who were 18 to 49 years of age (inclusive) at the time of vaccination in Study 307.

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

Table 2 Study 2019nCoV-312 Objectives and Endpoints

	Objectives	Endpoints
Primary	To characterize the Nab responses (geometric mean titers [GMTs]) to ancestral strain Novavax vaccine administered as a second (or subsequent) booster after licensed mRNA vaccines and a first ancestral strain Novavax vaccine booster.	• Nab GMTs to the ancestral strain SARS-CoV-2 at Day 29. Non-inferiority will be demonstrated if the lower-bound (LB) of the 95% CIs for the ratio of Nab GMT at Day 29 between the two booster periods is > 0.67. • If non-inferiority is demonstrated, results will be tested for superiority, defined as the LB of 95% CIs for the ratio of Nab GMT at Day 29 > 1.0.
Secondary	To further characterize the Nab responses (seroconversion rate [SCR]) to ancestral strain Novavax vaccine administered as a second (or subsequent) booster after licensed mRNA vaccines and a first ancestral strain Novavax vaccine booster. .	Proportion of participants who achieve seroconversion (≥ 4-fold increase from baseline) in neutralization antibody titers to the SARS-CoV-2 at Day 29 compared with results of the same measurements in participants who received their first ancestral strain Novavax vaccine booster after mRNA vaccination in Study 307. Non-inferiority will be demonstrated if the LB of the 95% exact CIs for the difference of SCRs in Nab titers is higher than –10%
	To demonstrate the noninferior immunogenicity of Novavax vaccine as a second (or subsequent) booster vs as a first booster of ancestral strain Novavax vaccine boost following mRNA vaccines.	• IgG geometric mean enzyme-linked immunoassay (ELISA) unit concentrations (GMEU/mL) to the SARS-CoV-2 ancestral strain spike protein at Day 29; Non-inferiority will be demonstrated if the lower-bound (LB) of the 95% CIs for the ratio of IgG GMEU at Day 29 between the two booster periods is > 0.67. • If non-inferiority is demonstrated, results will be

Table 2 Study 2019nCoV-312 Objectives and Endpoints

	Objectives	Endpoints
		tested for superiority, defined as a lower 95% confidence interval of GMEU ratio >1.0. • Proportion of participants who achieve seroconversion (≥ 4-fold increase from baseline) in IgG concentrations to the SARS-CoV-2 ancestral strain spike protein at Day 29 compared with results of the same measurements in participants who received their first ancestral strain Novavax vaccine booster after mRNA vaccination in Study 307. Non-inferiority will be demonstrated if the LB of the 95% exact CIs for the difference of SCRs in IgG ELISA unit is higher than –10%.
	To characterize the cross-reaction of neutralizing and IgG antibodies induced by the ancestral strain Novavax vaccine to more recent SARS-CoV-2 variants and any other variants for which appropriate assays are available.	Post-booster neutralizing GMTs and IgG GMEUs compared with post-first booster results from Study 307.
	To further characterize antibody responses in a human angiotensin-converting enzyme 2 (hACE2) receptor binding inhibition assay to the SARS-CoV-2 ancestral strain spike protein using the same calculations and comparison group as noted above for neutralizing and IgG antibodies.	Seroresponse data from Study 307 participants enrolled to the second treatment group of this study to receive an updated Novavax vaccine based on recent variant will be assayed using the same assays as described above. hACE2 antibodies post-updated booster will be compared to those post-ancestral strain boosters and will be analyzed in the same manner specifically to assess reactivity with the ancestral strain virus/spike protein and with recent variant virus/spike protein.
	To describe the overall safety of ancestral strain and updated (if administered) Novavax vaccine(s) administered as a second (or subsequent) booster following licensed mRNA vaccines and a first ancestral strain Novavax vaccine booster.	• Incidence, duration, and severity of solicited adverse reactions in the 7 days following study vaccination. • Incidence, duration, severity, and relationship of medically attended adverse events

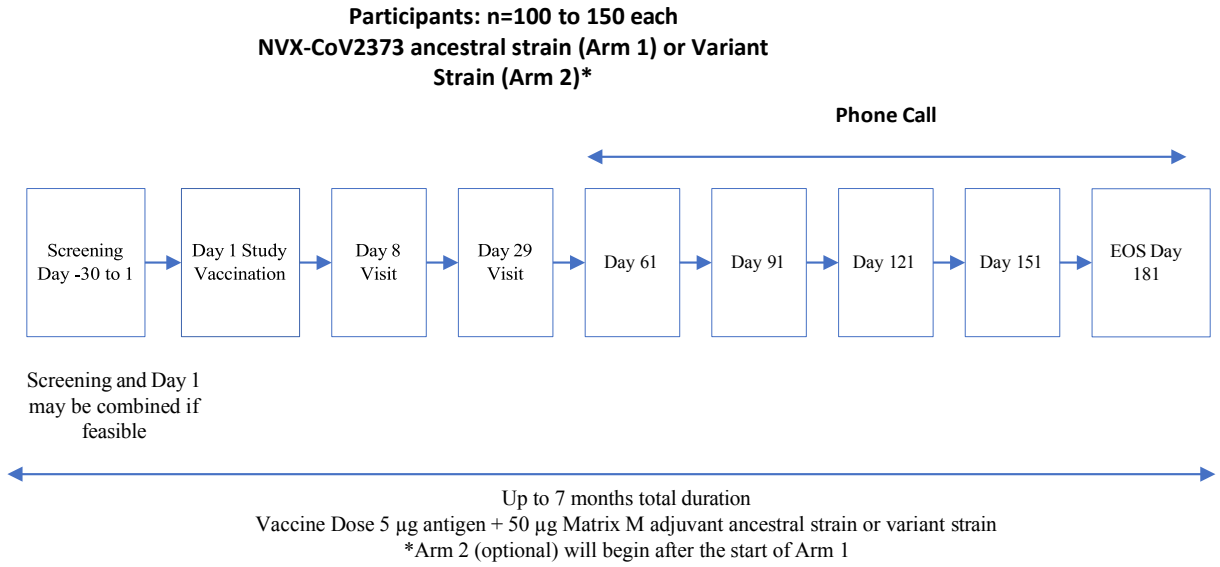
Table 2 Study 2019nCoV-312 Objectives and Endpoints

	Objectives	Endpoints
		(MAAEs) and adverse events of special interest (AESIs), (including myocarditis and/or pericarditis) through Day 180 after the vaccine dose. • Incidence and relationship of serious adverse events (SAEs) through Day 180 after the vaccine dose.
Exploratory	To utilize additional assays (current or to be developed) to best characterize the immune response for future vaccine development needs, including testing against emerging variants of SARS-CoV-2.	Additional endpoints to evaluate immune responses may be developed based on the assays used.

4 Study Plan

4.1 Study Schematic

Figure 1 Flow Diagram of Study 2019nCoV-312



4.2 Study Design

This is a Phase 3 study assessing the immunogenicity and safety of Novavax vaccine with Matrix-M adjuvant (NVX-CoV2373) as a booster dose following primary vaccination with authorized/approved mRNA vaccines (with or without subsequent mRNA booster) and one booster dose of NVX-Co2373. The study will enroll up to 300 previously vaccinated and boosted adults 18 to 49 years (inclusive) of age at the time of vaccination in Study 307.

Participants will be recruited from individuals who previously participated in Study 307 (received mRNA vaccine priming with or without a subsequent mRNA booster and an NVX- CoV2373 booster dose in Study 307).

Participants will receive 1 dose of study vaccine, given on Day 1, at a dose level of 5 µg of rS antigen with 50 µg of Matrix-M adjuvant.

All participants will remain on study for immunogenicity at Day 29 and safety data collection through 180 days following the vaccination.

4.3 Design Rationale

The purpose of this study is to assess safety and immunogenicity of ancestral strain NVX- CoV2373 and an updated Novavax vaccine based on recent variant(s), if administered, when used as a second booster dose in individuals who have previously received primary vaccine series with or without a booster dose of licensed mRNA vaccines followed by one booster with ancestral strain NVX-CoV2373 vaccine.

5 Population

5.1 Recruitment

Qualified participants from Study 307 who received 2 or 3 doses of an mRNA vaccine prior to Study 307 then one dose of ancestral strain NVX-CoV2373 during Study 307 will be screened in order to enroll up to 300 participants. These participants may be enrolled in 2 groups of 100 to 150 participants each, the first to receive the ancestral strain vaccine and the second, if enrolled, to receive an alternate vaccine based on a more recent variant of the SARS-CoV-2 virus. Participants will be enrolled to the 2 groups in a non-randomized fashion; the alternative treatment group, if initiated, will be conducted in staggered fashion after enrollment in the ancestral strain group has begun.

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 the following criteria:

1. Adults 18 to 49 years (inclusive) of age at the time of vaccination in Study 307 who received two or three doses of mRNA prior to enrollment in Study 307, then one dose of ancestral strain NVX-CoV2373 in Study 307.
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 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 COVID-19 vaccines. The most recent dose of NVX-CoV2373 must have been administered at least 180 days prior to vaccination in this study.

5.4 Exclusion Criteria

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

1. Received any additional COVID-19 vaccine booster after the Day 1 dose of NVX-CoV2373 administered during participation in Study 307.
2. History of laboratory-confirmed (by polymerase chain reaction [PCR] or rapid antigen test) COVID-19 infection ≤ 4 months prior to Day 1.
3. Current participation in research involving receipt of an investigational product (drug/biologic/device).
4. Any known allergies or history of anaphylaxis to the active substance or any of the other ingredients contained in the investigational product.
5. Any autoimmune or immunodeficiency disease/condition (iatrogenic or congenital) or therapy that causes clinically significant immunosuppression.
6. 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.
7. 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.
8. 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).
9. Participants who are breastfeeding, pregnant, or who plan to become pregnant prior to the EOS visit.
10. 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.
11. 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).
12. 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).
13. Participants with a history of myocarditis or pericarditis.

6 Study Conduct

This is a Phase 3 study comparing the immunogenicity and safety of Novavax vaccine(s) with Matrix-M adjuvant (ancestral strain NVX-CoV2373 and an alternative strain and/or multivalent Novavax vaccine) as booster doses following a series of primary and booster doses of authorized/approved mRNA vaccines followed by a single booster dose of NVX-CoV2373 in Study 307.

Following vaccination, all participants will remain on study for immunogenicity on Day 29 and safety data collection through Day 181 (EOS).

6.1 Study Procedures

6.1.1 Screening Period

The following activities will occur at the Screening Visit. The Screening Visit may occur up to 30 days prior to Day 1, but can be and is expected to be combined with the Day 1 Visit when possible.

- Informed consent
- Medical history, including prior and concurrent medical conditions and significant surgical procedures in the 6 months prior to enrollment. Significant medical history should be recorded, focusing on ongoing medical conditions.
- 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. All COVID-19 vaccines must be recorded, including type and dates of receipt. Concomitant medications include prescription and over-the-counter (OTC; including vaccines) medications taken by the participant during the study. Do not record herbals, vitamins, and/or 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 (WOCBP). A positive test will result in screen failure.
- Physical examination at screening to include height and weight, cervical and axillary lymph nodes, heart, and any other symptom-directed (targeted) examination.
- Recording of SAEs following signing of informed consent.

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 WOCBP. A positive test will result in disqualification.
- Baseline electrocardiogram (ECG)
- Physical examination, to include cervical and axillary lymph nodes, heart, and any other symptom-directed (targeted) examination.
- Nasal swab at clinic for SARS-CoV-2 (PCR)—anterior nares
- Blood sampling for anti-NP testing
- Blood sampling for SARS-CoV-2 (ELISA for anti-S protein serology, Nab titers, and hACE2 receptor-binding inhibition assay)
- Vaccination
- Distribution of the diary to the participants, including a review of how to complete the diary with the participant
- Recording of solicited (reactogenicity) and unsolicited AEs, SAEs, MAAEs, and AESIs (including potential immune-mediated medical conditions [PIMMCs] and myocarditis or pericarditis). See Table 3 for symptoms of myocarditis or pericarditis and Table 4 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 Day 8 Visit

The following activities will occur at the Day 8 visit:

- The diary that participants use to record reactogenicity data between Days 1 and 7 will be reviewed with the participants and collected so that site personnel can record the information by electronic data capture (EDC).
- Recording of unsolicited AEs, SAEs, MAAEs, and AESIs (including PIMMCs and myocarditis or pericarditis). See Table 3 for symptoms of myocarditis or pericarditis and Table 4 for instructions for follow-up.
  NOTE: Should any reactogenicity event extend beyond 7 days after vaccination (toxicity grade ≥ 1), then it will be recorded as an AE with the same start date as the reactogenicity event and followed to resolution.

6.1.4 Day 29 Visit

The following activities will occur at the Day 29 visit.

- Prior/concomitant medications
- Blood sampling for SARS-CoV-2 (ELISA for anti-S protein serology, Nab titers, and hACE2 receptor-binding inhibition assay)
- Blood sampling for anti-NP testing
- Recording of unsolicited AEs, SAEs, MAAEs, and AESIs (including PIMMCs and myocarditis or pericarditis). See Table 3 for symptoms of myocarditis or pericarditis and Table 4 for instructions for follow-up.

6.1.5 Days 61, 91, 121 and 151 (Phone Call)

Participants will receive a phone call and the following information will be collected:

- Prior/concomitant medications or vaccines that may have caused or are used to treat an AE. All COVID-19 vaccines received during the study should be recorded.
- Recording of SAEs, MAAEs attributed to study vaccine, and AESIs (including PIMMCs, myocarditis or pericarditis). See Table 3 for symptoms of myocarditis or pericarditis and Table 4 for instructions for follow-up.

6.1.6 Day 181 (End of Study Phone Call)

The following activities will be performed at the EOS Phone Call. .

- Prior/concomitant medications or vaccines that may have caused or are used to treat an AE.
- Recording of SAEs, MAAEs attributed to study vaccine, and AESIs (including PIMMCs, myocarditis or pericarditis). See Table 3 for symptoms of myocarditis or pericarditis and Table 4 for instructions for follow-up.
- Completion of EOS form

6.1.7 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 the visit, the following procedures will be performed:

- Prior/concomitant medications or vaccines that may have caused or are used to treat an AE.
- Vital signs measurement including respiratory rate, blood pressure, pulse rate, and temperature (oral or via forehead/ear reader)
- Physical examination – symptom directed (targeted)
- Recording of SAEs, AE/MAAEs, and AESIs (including PIMMCs, myocarditis or pericarditis) per reporting timelines outlined in Table 1. See Table 3 for symptoms of myocarditis or pericarditis and Table 4 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 in order to collect a blood sample at Day 29 and to conduct safety follow-up through Day 181. In cases where the participant is not able to visit the study site for the Day 29 visit, participant contact for safety follow-up 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

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 remote contacts; eg, 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 letter that can be tracked to ensure delivery. 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.

6.2.1.3 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.

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 intramuscular (IM) injection (Day 1) of 0.5 mL injection volume with a total dose of 5 µg recombinant rS antigen with 50 µg Matrix M adjuvant. Vaccine will be administered as an open-label material.

Vaccine	Baseline Serostatus	Number of Doses	Number of Participants	Dose (antigen/ Matrix-M adjuvant)
Ancestral strain NVX-CoV2373	Previously vaccinated	1	100-150	5 µg / 50 µg
Updated Novavax COVID-19 Vaccine based on recent variant(s)	Previously vaccinated	1	100-150	5 µg / 50 µg

7.1 Description of Products

7.1.1 NVX-CoV2373 Ancestral Strain

7.1.1.1 Formulation, Storage, Preparation, and Handling

NVX-CoV2373 ancestral strain 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 administered according to standard practice by qualified study site personnel as described in the Pharmacy Manual.

7.1.2 Updated Novavax COVID-19 Vaccine Based on Recent Variant(s)

7.1.2.1 Formulation, Storage, Preparation, and Handling

The Updated Novavax COVID-19 vaccine will be supplied as a solution for preparation for injection of SARS-CoV-2 rS antigen at a concentration of 10 μg/mL and Matrix-M adjuvant at a concentration of 100 μg/mL.

The Updated Novavax COVID-19 vaccine 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. Description of its preparation can be found in the Pharmacy Manual.

7.1.2.2 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.

7.1.2.3 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 as described in the Pharmacy Manual.

7.2 Treatment Assignment and Bias Minimization

7.2.1 Treatment Allocation

As this is an open-label trial, a log of the participant ID number with the treatment vial administered will be completed at the site and will be held by Syneos Health during the study.

7.2.2 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. The vial number of the vaccine will be recorded for each study participant. 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.

7.3 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 Day 29 (or through the early termination visit if prior to that time). Prescription and OTC drugs will be included. Do

not record herbals, vitamins, and supplements. After Day 29, concomitant medications that may have caused or are being used to treat an AE should be recorded.

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. Any COVID-19 vaccine received from Day 30 until EOS should be recorded.

7.3.1 Prohibited Therapies

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

- Any COVID-19 vaccines during the course of the study.
- Seasonal influenza vaccine may not be administered < 4 days before or < 7 days after the study vaccine.
- All other vaccines, except rabies vaccine (if medically indicated), ≤ 90 days before enrollment until Day 29.
- Investigational product (drug/biologic/device) from time of enrollment until after the last study visit.
- 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).

Solicited (reactogenicity) and unsolicited AEs will be graded for severity using the provided criteria (Appendix 3). Recording of solicited and unsolicited AEs will be conducted by EDC. AESIs, including PIMMCs, myocarditis and/or pericarditis (see Table 3), and complications specific to COVID-19, will also be monitored (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.

8.1 Definitions

- **Adverse event** – An AE is any untoward medical occurrence associated with the use of an intervention in humans whether or not it is considered intervention-related. Any abnormal laboratory test results or other safety assessments (eg, physical examination, vital signs measurements) that are clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease) will be considered AEs. An exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity, will be considered an AE.
- **Serious adverse event (SAE)** – An event is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:
  - Death
  - A life-threatening AE (an event is considered "life-threatening" if, in the view of either the investigator or Sponsor, its occurrence places the patient or participant at immediate risk of death. It does not include an AE or suspected adverse reaction (AR) that, had it occurred in a more severe form, might have caused death.)
  - Inpatient hospitalization or prolongation of existing hospitalization. In general, hospitalization signifies that the participant has been detained, usually involving an overnight stay, at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an SAE.
  - A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
  - A congenital anomaly/birth defect
  - Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room (ER) or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

- **Causality or relatedness** – For each AE/SAE, the Investigator must document in the medical notes that 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 drug caused the AE. For the purposes of 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. Unexpected also refers to events that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.
- **Severity or intensity** –The severity (or intensity) of an AE/SAE refers to the extent to which it affects the participant's daily activities and will be classified as mild, moderate, or severe using the following criteria:
  - Mild: These events require minimal or no treatment and do not interfere with the participant's daily activities.
  - Moderate: These events result in a low level of inconvenience or require minor therapeutic measures. Moderate events may cause some interference with normal functioning.
  - Severe: These events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

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

8.1.1 Documenting Adverse Events

At every study visit and phone call, participants will be asked to report any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any

accidents, used any new medications that may have caused or were used to treat an adverse event, or changed concomitant medication regimens (both prescription and OTC medications).

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

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

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

8.1.2 Details of the Adverse Event

8.1.2.1 Assessment of Causality

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

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

- Time relationship between study vaccine injection and event's onset.
- Medical history.
- Study treatment.
- Mechanism of action of study vaccine.

- Class effect.
- Concomitant treatments in use.
- Withdrawal of study treatment.
- Lack of efficacy/worsening of existing condition.
- Possible vaccine enhancement of COVID-19.
- Erroneous treatment with study medication or concomitant medication.
- Protocol-related process.

8.1.2.2 Action Taken with Study Vaccine due to Adverse Event

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

- No action taken
- Not applicable

8.1.2.3 Other Action Taken

Details of any other actions taken should be specified:

- Specific therapy/medication
- Surgical or medical procedure
- Prolonged hospitalization

8.1.2.4 AE Outcome

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

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

8.1.3 Timeframe for Collection

All AEs captured following the procedures listed in the SOE (Table 1) 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 unsolicited AEs of any severity will be collected from the time of study vaccination through 28 days after study vaccination. After Day 29, unsolicited AEs classified as MAAEs attributed to study vaccine will be collected until EOS.

All AESIs/PIMMCs will be collected from the time of study vaccination through 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.

8.1.4 Classification of Events

8.1.4.1 Treatment-Emergent Adverse Event

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

8.1.4.2 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. All AESIs must be reported within 24 hours of site awareness to Novavax Global Vaccine Safety on the SAE/AESI form. Listings of AESIs are presented in Appendix 2.

8.1.4.2.1 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 3) 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 preferably by a cardiologist 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 4). A Central Cardiac Adjudication Committee has been established to adjudicate possible myocarditis and/or pericarditis cases in the clinical development plan of NVX-CoV2373. Outcomes of the adjudications will be communicated 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 3 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 myocarditis2 • Abnormal cardiac function or wall motion abnormalities on echocardiogram • cMRI findings consistent with myocarditis3 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 myocarditis4 • cMRI findings consistent with myocarditis3 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 pericarditis5	Presence of ≥ 2 new or worsening of the following clinical features: • Acute chest pain6 • 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 4 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 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.

8.1.4.2.2 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 that constitutes a possible case of myocarditis and/or pericarditis at any time during the study that requires review by the Cardiac Adjudication Committee.

8.1.4.3 Medically Attended Adverse Events

An MAAE is defined as an AE that leads to an unscheduled visit to a healthcare practitioner. All MAAEs will be reported from the time of study vaccination through Day 29. After Day 29, MAAEs attributed to study vaccine will be captured until EOS.

8.1.4.4 Reactogenicity Symptoms

On the day of vaccination, participants will remain in clinic (or under observation) for at least 15 minutes to be observed for any immediate reaction. Injection site specific local and general systemic reactogenicity reactions including start and stop dates will be recorded following vaccination. Any immediate reaction will be recorded as an AE on day of vaccination.

Participants will utilize their diary to record reactogenicity for the 7 days following vaccination. All participants will record reactogenicity starting on the same day of the vaccination and for a total of 7 days. Should any reactogenicity event extend beyond 7 days after vaccination (toxicity Grade ≥ 1), then it will be recorded as an AE with a start date that matches Day 8 of the reactogenicity event and followed to resolution per FDA guidelines for AE capture. The toxicity grading scale implemented in the diary is included in Appendix 3.

8.2 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 Novavax representatives of any SAE that occurs during the course of the study, from the time of informed consent until the EOS visit, regardless of whether it is judged to be causally related to study vaccine or procedures. Notification must occur within 24 hours of when they become aware of it. AESIs, including PIMMC, myocarditis or pericarditis and 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 Novavax Global Vaccine Safety within 24 hours as described above. The date when the AE becomes serious should be notated in the eCRF and on the SAE form.

All SAEs and AESIs will also be recorded in the eCRF and the paper SAE/AESI form. The investigator is responsible for informing the Institutional Review Board (IRB) of the SAE as per local requirements.

Paper SAE forms should be completed at the study site, signed (physically or electronically) by the Investigator or a qualified Sub-Investigator and emailed within 24 hours of study site awareness of the event to the Novavax Global Vaccine Safety mailbox:

Safety@novavax.com

The SAE form should be attached to the email; a notification email of the event describing it in the email text is not sufficient. There may be situations when an SAE has occurred, and the investigator has minimal information to include in the initial SAE report. However, it is very

important that the investigator always makes an assessment of causality for every event prior to transmission of the SAE report form.

Minimum criteria for a reportable event are:

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

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

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

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

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

8.3 Pregnancy

Pregnancy is not considered an AE unless there is a suspicion that an investigational vaccine may have interfered with the effectiveness of a contraceptive medication. Any pregnancy that occurs during study participation must be reported using the Pregnancy reporting form. To ensure participant safety, each pregnancy must be reported to Novavax Global Vaccine Safety 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 completion or after the participant has completed the study but occurring while the participant was enrolled in the study must be promptly reported to Novavax Global Vaccine Safety: Safety@novavax.com using the pregnancy reporting forms provided to the sites.

8.4 Overdose

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 Novavax Global Vaccine Safety within 24 hours of awareness, using the details provided in Section 9.3 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 need 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.

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, Nab responses to ancestral strain Novavax vaccine administered as a second (or subsequent) booster after licensed mRNA vaccines and a first ancestral strain Novavax vaccine booster).

MN50 data from Novavax's Study 2019nCoV-301 of around 240 adult participants who received the SARS-CoV-2 rS vaccine on Day 0 and Day 21 in the initial period of primary series or crossover period then received boost dose at Day 0 in the booster period exhibited an 80% confidence upper bound of standard deviation of MN50 GMFR between 28 days after the third active (booster) dose and 14 days after 2nd active dose in log10 scale of 0.61.

The sample size (Table 5) is based on providing at least 90% power to conclude non-inferiority on Nab titers given the null hypothesis of GMFR (GMTDay29-312/GMTD29-307) ≤ 0.67. Here, GMTDay29-312 is Nab GMT at Day 29 from 2019nCoV-312 and GMTDay29-307 is Nab GMT at Day 29 from Study 307. It is anticipated that these estimates will be equally applicable in the event that a different assay of Nab titers is used for this study.

Table 5 Summary of Sample Size

GMFR	N
1.0	129
1.1	85
1.2	62
1.3	49
1.4	40
1.5	34

Abbreviation: GMFR=geometric mean fold rise; N=number

9.2 Analysis Subsets

The following analysis sets are identified for analysis.

9.2.1 Selected Participants Analysis Set

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

9.2.2 Full Analysis Set

The full analysis set (FAS) will include all participants who are 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 enrolled. 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 receive a 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, enrolled, and vaccinated will be presented by the study vaccine group for the Selected Participants Analysis Set.

The number (percentage) of participants in the Selected Participants Analysis Set, FAS, Safety Analysis Set, and PP Analysis Set who have completed the study (from Day 1 through Day 181) will be summarized 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 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.

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 will be summarized 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.

The time between last dose of previous COVID-19 vaccination and Day 1 vaccination dose may be summarized for the study vaccine group(s) using descriptive statistics.

9.3.2 Immunogenicity Analyses

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

For the primary endpoint of Nab responses to the ancestral strain Novavax vaccine administered as a second (or subsequent) booster after licensed mRNA vaccines and a first ancestral strain Novavax vaccine booster, Nab GMTs at Day 1 and Day 29 will be summarized for the group receiving the ancestral strain Novavax vaccine. Nab GMTs along with the corresponding 2-sided 95% CIs, are calculated by exponentiating the corresponding log-transformed means and their 95% CIs. GMFR is defined as the ratio of Nab titers within the group of ancestral strain Novavax vaccine between two different time-points (Day 29 vs. Day 1) to be conducted using t distribution on the log-transformed ratio. Ratio of Nab GMTs for the group receiving the ancestral strain Novavax vaccine between 28 days post first dose (at Day 29) in Study

2019nCoV-312 and 28 days post first dose (at Day 29) in Study 307 among the same participants will be conducted using t distribution on the log-transformed ratio to evaluate non-inferiority. Non-inferiority will be demonstrated if the LB of the 95% CIs for the ratio of Nab GMT at Day 29 between the two booster periods is > 0.67. If non-inferiority is demonstrated, results will be tested for superiority, defined as the LB of 95% CIs for the ratio of Nab GMTs at Day 29 > 1.0.

For the secondary endpoint of Nab responses to ancestral strain Novavax vaccine administered as a second (or subsequent) booster after licensed mRNA vaccines and a first ancestral strain Novavax vaccine booster, the proportion of participants in the group receiving ancestral strain Novavax vaccine who achieve seroconversion (≥ 4-fold increase from baseline) in Nab titers to the SARS-CoV-2 at Day 29 defined as SCR will be calculated. SCR in Nab titers with corresponding 2-sided exact binomial 95% CIs will be calculated using the Clopper-Pearson method. Two-sided 95% CIs of the difference of SCRs in Nab titers for the group receiving the ancestral strain Novavax vaccine between 28 days post first dose (at Day 29) in Study 2019nCoV-312 and 28 days post first dose (at Day 29) in Study 307 among the same participants will be based on the method of confidence interval (CI) for the difference in two correlated proportions by Tango (the method of Tango CIs will be described in the Statistical Analysis Plan). Non-inferiority will be demonstrated if the LB of the 95% exact CIs for the difference of SCRs in Nab titers is higher than –10%.

For the secondary endpoints of noninferior immunogenicity of the Novavax vaccine as a second (or subsequent) booster vs as a first booster of ancestral strain Novavax vaccine boost following mRNA vaccines, IgG geometric mean enzyme-linked immunoassay (ELISA) unit concentrations (GMEU/mL) to the SARS-CoV-2 ancestral strain spike protein for the group receiving ancestral strain Novavax vaccine at Day 1 and Day 29 will be calculated. IgG GMEU along with the corresponding 2-sided 95% CIs is calculated by exponentiating the corresponding log-transformed means and their 95% CIs. GMFR is defined as the ratio of IgG GMEUs within the group receiving the ancestral strain Novavax vaccine; An analysis of the study vaccine group between two different time-points (Day 29 vs. Day 1) will be conducted using t distribution on the log-transformed ratio. The ratio of IgG GMEUs for the group receiving the ancestral strain Novavax vaccine between 28 days post first dose (at Day 29) in Study 2019nCoV-312 and 28 days post first dose (at Day 29) in Study 307 among the same participants will be conducted using t distribution on the log-transformed ratio to evaluate non-inferiority. Non-inferiority will be demonstrated if the lower-bound (LB) of the 95% CIs for the ratio of IgG GMEU at Day 29 among the same participants between the two booster periods is higher than 0.67. If non-inferiority is demonstrated, results will be tested for superiority, defined as a lower 95% CI for the ratio of IgG GMEUs at Day 29 > 1.0. The proportion of participants in the group receiving the ancestral strain Novavax vaccine who achieve seroconversion (≥ 4-fold increase from baseline) in IgG concentrations to the SARS-CoV-2 ancestral strain spike protein at Day 29 is defined as the SCR. SCR in IgG GMEUs with corresponding two-sided exact binomial 95% CIs will be calculated using the Clopper-Pearson method. Two-sided 95% CIs of the difference of SCRs in IgG GMEUs for the group receiving the ancestral strain Novavax vaccine between 28 days post first dose (at Day 29) in Study 2019nCoV-312 and 28 days post first dose (at Day 29) in Study 307 among the same participants will be calculated using the method of CI for the

difference in two correlated proportions by Tango. Non inferiority will be demonstrated if the LB of the 95% exact CIs for the difference of SCRs in IgG GMEUs is higher than –10%.

For the secondary endpoints of cross-reaction of neutralizing and IgG antibodies induced by the ancestral strain Novavax vaccine to more recent SARS-CoV-2 variants for which appropriate assays are available, post-booster neutralizing GMTs, IgG GMEU, and GMFR for the group receiving updated NVX-CoV2373 based on recent variant(s) will be obtained using the methods noted above. Ratio of Nab GMT, difference of SCRs in Nab titers, ratio of IgG GMEUs, and differences in SCRs in IgG GMEUs for the group receiving the updated NVX-CoV2373 vaccine based on recent variant(s) is to be calculated among the same participants from Study 307.

For the secondary endpoints of antibody responses in a human angiotensin-converting enzyme 2 (hACE2) receptor binding inhibition assay to the SARS-CoV-2 ancestral strain spike protein, the same statistical methods applied for the analysis of Nabs will be applied to hACE2,b including GMT, ratio of GMT, SCR, and difference in SCRs for the group receiving ancestral strain Novavax vaccine.

For the exploratory objective of utilizing additional assays (current or to be developed) to best characterize the immune response for future vaccine development needs, including testing against emerging variants of SARS-CoV-2, the same statistical methods applied for Nab, IgG or hACE2 may be applied to evaluate immune responses based on the assays used.

9.3.3 Safety Analyses

To describe the overall safety of ancestral strain and updated (if administered) Novavax vaccine(s) administered as a second (or subsequent) booster following licensed mRNA vaccines and a first ancestral strain Novavax vaccine booster, the secondary endpoints of safety data include solicited AEs in the 7 days following study vaccination and MAAEs, AESIs (including myocarditis and/or pericarditis), and SAEs throughout the study. All safety analyses will be descriptive and conducted using the Safety Analysis Set.

All local/systemic solicited (reactogenicity) AEs within the post-vaccination window (Days 1-7) by the verbatim terms, and by severity (mild, moderate, severe) using the maximal severity observed for the specific symptom post-vaccination will be summarized for each study vaccine group.

Unsolicited MAAEs, AESIs (including myocarditis and/or pericarditis), and SAEs throughout the study will be summarized 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, AESIs, and SAEs through Day 181 will also be summarized.

A by-participant listing of MAAEs, AESIs, 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 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 prior and 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. A by-participant listing of vital signs will be provided.

9.3.3.3 Physical Examinations

Physical examination at Screening or Day 1 will include height and weight, cervical and axillary lymph nodes, and heart, and any other areas based on participant symptoms. A targeted examination will be performed at unscheduled visits.

9.4 Interim Analyses

The 1st interim analysis will be performed when the complete data for Nab titers and/or IgG GMEUs and/or hACE2 titers for the ancestral strain Novavax vaccine and safety data from Day 1 through Day 29 are available.

The 2nd interim analysis will be performed when the complete data for Nab titers and/or IgG GMEUs and/or hACE2 titers for an updated Novavax vaccine are available.

The first and second interim analysis may be combined into one analysis depending on when the ancestral strain arm of the study and the updated Novavax vaccine arm are executed.

9.5 Final Analysis

The final analysis will be performed when safety data throughout the study (from Day 1 through EOS) 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 IRB and must be submitted/notified to the regulatory authority, as required, before they are implemented.

10.2 Ethics Review

Prior to the start of the study, the investigator is responsible for ensuring that the protocol and consent form have been reviewed and approved by a relevant IRB. The IRB shall be appropriately constituted and perform its functions in accordance with ICH GCP and local requirements as applicable.

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

10.3 Informed Consent

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

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

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

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

10.4 Data Privacy

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

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

11 Oversight

11.1 Quality Control and Assurance

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

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

The investigator will be responsible for the following:

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

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

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

11.1.1 Monitoring

The Syneos 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.

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

11.1.2 Audits

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

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

11.1.3 Protocol Deviations

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

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

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

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

11.1.4 Records

11.1.4.1 Data Capture and Management

All required study data will be entered by study site personnel in the eCRF or by study participants in the paper diary created for the study. Data required according to this protocol will be recorded by study site personnel via data entry into the internet-based EDC software system or by study participant via the 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, reactogenicity diaries and complete medical history and physical examination reports. All information in the CRF must be traceable to the participant's source documents.

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

11.1.4.3 Records Retention

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

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

11.2 Study Termination or Study Site Closure

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

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

12 Publication Policy

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

The Sponsor will generally support publication of multicenter studies only in their entirety and not as individual study site data. In this case, a coordinating investigator will be designated by mutual agreement. Authorship will be determined by mutual agreement and in line with the International Committee of Medical Journal Editors authorship agreements. Authors will be provided reasonable access to all study data, statistical tables, figures, and relevant reports and will have the opportunity to review complete study results. All proposed publications based on this study must be participant to the Sponsor's approval requirements.

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

13 Financing and Insurance

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

Neither the sponsor nor 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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Appendix 1 PROTOCOL CHANGE HISTORY

Protocol Version 2.1, 26 March 2025 (revised from Version 2.0, 23 February 2023)

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

Location of Change	Change/Modification in Version 2.1, 26 March 2025
Title Page	Administrative Change – Added the NCT to Clinical Trial Registry Identifiers

Protocol Version 2.0, 23 February 2023 (revised from Version 1.0, February 10, 2023)

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

Location of Change	Change/Modification in Version 2.0, 23 February 2023
Schedule of Events	Superscripted "1" on the Screening Day to correct error
Schedule of Events and Section 7.3	Changed "caused" to "may have caused" to description of concomitant medications to be recorded for consistency.
Figure 1	Removed "phone call" from flow diagram (Figure 1).
Schedule of Events footnote and throughout the document	Changed "Memory Aid" to diary for greater accuracy.
Table 7	Updated to another version

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

Complications 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).

APPENDIX 3 TOXICITY GRADING SCALE FOR CLINICAL ABNORMALITIES, (LOCAL AND GENERAL SYSTEMIC REACTOGENICITY, CLINICAL LABORATORY, AND VITAL SIGNS)

Table 8 FDA Toxicity Grading Scale for Local and General Systemic Reactogenicity

Local Reaction to Injectable Product				
Clinical Abnormality	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Pain	Does not interfere with activity	Repeated use of non-prescription pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/redness[a]	2.5 − 5 cm	5.1 − 10 cm	> 10 cm	For all participants: Necrosis or exfoliative dermatitis
Induration/swelling[b]	2.5 − 5 cm and does not interfere with activity	5.1 − 10 cm or interferes with activity	> 10 cm or prevents daily activity	For all participants: Necrosis
Systemic (General)				
	Mild (Grade 1)	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Fever[c] (°C)[c] (°F)	38.0 − 38.4 100.4 − 101.1	38.5 − 38.9 101.2 − 102.0	39.0 − 40 102.1 − 104	> 40 > 104
Nausea/vomiting	No interference with activity or 1 − 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, or requires outpatient IV hydration	Requires ER visit or hospitalization for hypotensive shock
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue/Malaise	No interference with activity	Some interference with activity	Significant, prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant, prevents daily activity	ER visit or hospitalization
Arthralgia	No interference with activity	Some interference with activity	Significant, prevents daily activity	ER visit or hospitalization

Abbreviations: DHHS = Department of Health and Human Services; ER = emergency room; FDA = United States Food and Drug Administration.

[a] In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

[b] Induration/swelling should be evaluated and graded using the functional scale as well as the actual measurement.

[c] Oral temperature; no recent hot or cold beverages.

Source: [DHHS 2007].