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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

Novavax Protocol Number: **2019nCoV-312**

STATISTICAL ANALYSIS PLAN (SAP) FOR
Interim/Final Analysis of Immunogenicity and Safety Data

SAP Version and Date: Version 4.0 –22AUG2023

Investigational Product:

- Ancestral strain NVX-CoV2373 (5 µg)
- Updated Novavax COVID-19 vaccine based on recent variant(s)

APPROVAL SIGNATURE PAGE

Protocol Number:	2019nCoV-312
Protocol Version and Date:	Version 2.0 (Amendment 1.0) – 23 February 2023
Protocol 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
SAP Version and Date:	Version 4.0 – 22 AUG 2023

☐ Original Statistical Analysis Plan

☒ Amended Statistical Analysis Plan

SAP Originated By: [redacted] 22 August 2023
Date

Signatures below indicate the SAP has been reviewed and approved by the following personnel:

Signed Electronically

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Signed Electronically

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Signed Electronically

[redacted]

SAP CHANGE HISTORY

SAP Version 3.0, 16 May 2023 (revised from Version 2.0, 03 March 2023)

The following is a summary of the changes made to this SAP.

Location of Change	Change/Modification in Version 3.0
Section 3.2, Section 3.5, Section 4 and Section 5	Remove the analysis per FAS due to the change of enrollment procedure, that is, subjects to be dosed with ancestral strain NVX-CoV2373 are enrolled first and subjects to be dosed with updated Novavax COVID-19 Vaccine based on recent variant(s) are enrolled afterward.
Section 7.2.1	Clarify SCR definition for Nab titers per CBER comments: SCR is defined as proportion of participants who achieve seroconversion ≥ 4-fold increase from baseline in Nab titers at Day 29 if the baseline value is equal to or above LLOQ or at least 4-fold fold rise from LLOQ if the baseline value is lower than LLOQ
Section 7.2.2	Clarify SCR definition for ELISA (IgG) ELISA Units per CBER comments: SCR is defined as proportion of participants who achieve seroconversion ≥ 4-fold increase from baseline in IgG GMEUs at Day 29 if the baseline value is equal to or above LLOQ or at least 4-fold fold rise from LLOQ if the baseline value is lower than LLOQ
Section 7.2.3	Clarify SCR definition for hACE2 titers per CBER comments: SCR is defined as proportion of participants who achieve seroconversion ≥ 4-fold increase from baseline in hACE2 titers at Day 29 if the baseline value is equal to or above LLOQ or at least 4-fold fold rise from LLOQ if the baseline value is lower than LLOQ
Section 7.3.1	Clarify the grading of solicited AEs, especially Grade 4 for redness and swelling
Section 7.3.2	Delete the period of Days 29 – 181
Table 11	Add the missing 3rd to 6th footnotes
References	Add one missing reference (FDA 2007) for Table 10 and three missing references (Ferreira 2018, Adler 2015, and Gargano 2021) for Table 11.

SAP Version 4.0, 22 August 2023 (revised from Version 3.0, 22 May 2023)

The following is a summary of the changes made to this SAP.

Location of Change	**Change/Modification in Version 4.0**
Section 1.2, 7.1, 7.2 and 11	Change the terminology from $GMFR_{312/307}$ to $GMR_{312/307}$
Section 7.2.1	Add the statements of the conversion from the values of Pseudovirus-based Nab response (Wuhan) in ID50 tested by Monogram for Study 2019nCoV-307 and those tested by NVX CI for Study 2019nCoV-312 to the values in the standard unit of IU/mL. Clarify the summary of Pseudovirus-based Nab response per Wuhan and Omicron BA.5 strain since Pseudovirus-based Nab response per Omicron BA.5 was not tested in Study 2019nCoV-307.
Section 7.2.2	Clarify the summary of IgG per Wuhan and Omicron BA.5 strain
Section 7.2.3	Clarify the summary of hACE2 per Wuhan and Omicron BA.5 strain due to no data of hACE2 per Omicron BA.5 strain from Study 2019nCoV-307.
Section 12 Reference	Add one Monogram report as the reference of the conversion factor (0.1458) Add one NVX CI PNA validation report as the reference of the conversion factor (0.214).

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
ANCA	Anti-neutrophil cytoplasmic antibody
ARDS	Acute respiratory distress syndrome
ATC	Anatomical therapeutic chemical
BMI	Body mass index
CI	Clinical Immunology
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CRO	Clinical research organization
CSR	Clinical Study Report
DAIDS	Division of AIDS
Division of AIDS	Division of AIDS
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
ELISA	Enzyme-linked immunosorbent assay
EOS	End of Study
ELISA	ELISA
FAS	Full Analysis Set
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
GMEU	Geometric mean ELISA unit
GMFR	Geometric mean fold rise
GMT	Geometric mean titer
hACE2	Human angiotensin-converting enzyme 2
HEENT	head nose ears and throat
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IgG	Immunoglobulin G
IRB	Institutional Review Board
MAAE	Medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MN_{50}	Microneutralization assay with an inhibitory concentration of 50%
OTC	Over the counter
PCR	Polymerase chain reaction

Abbreviation	Definition
PIMMC	Potential immune-mediated medical conditions
PP	Per-Protocol
PT	Preferred term
Rs	Recombinant spike
S	Spike (protein)
SAE	Serious adverse event
SARS-CoV	Severe acute respiratory syndrome coronavirus
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SCR	Seroconversion rate
SII	Serum Institute of India
SOC	System organ class
SOE	Schedule of Events
SOP	Standard Operating Procedure
TEAE	Treatment-emergent adverse event
TGS	Toxicity grading scale
US	United States

1 INTRODUCTION

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). NVX-CoV2373 is the ancestral strain SARS-CoV-2 rS nanoparticle vaccine construct adjuvanted with Matrix-M™ adjuvant that is authorized 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 and adolescents 12 – 17 years of age. The investigational products used in this study are manufactured by Serum Institute of India (SII) through a partnership with Novavax.

Supportive clinical data are available via studies conducted using Novavax manufactured SARS-CoV-2 rS products. The clinical development program for Novavax's SARS-CoV-2 rS with Matrix-M adjuvant comprises 4 ongoing clinical studies: a Phase 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 subjects 12 to < 18 years of age (Study 2019nCoV-301) and 18 to 84 years of age (Study 2019nCoV-302). Additionally, Study 2019nCoV-307, which confirmed the lot-to-lot consistency of three manufacturing lots also looked at the effect of homologous and heterologous boosting with NVX-CoV2373 in adults ≥ 18 – 49 years of age and forms the basis for this study and its enrollment population.

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 immune response following heterologous and homologous boosting with respect to 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.

The purpose of this study is to assess immunogenicity and safety of ancestral strain NVX-CoV2373 and, possibly, an updated Novavax vaccine based on recent variant(s), when used as a second or subsequent booster dose in individuals who previously received primary vaccine series of licensed mRNA with or without a subsequent mRNA booster dose followed by one booster with ancestral strain NVX-CoV2373 vaccine who were 18 to 49 years of age at the time of vaccination in Study 2019nCoV-307.

1.1 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-CoV2373. The study will enroll up to 300 previously vaccinated and boosted adults 18 to 49 years of age at the time of vaccination in Study 2019nCoV-307 (Table 1).

Participants will be recruited from individuals who previously participated in Study 2019nCoV-307 (received mRNA vaccine priming with or without a subsequent mRNA booster and an NVX-CoV2373 booster dose in the 307 study).

Table 1: Study Vaccinations

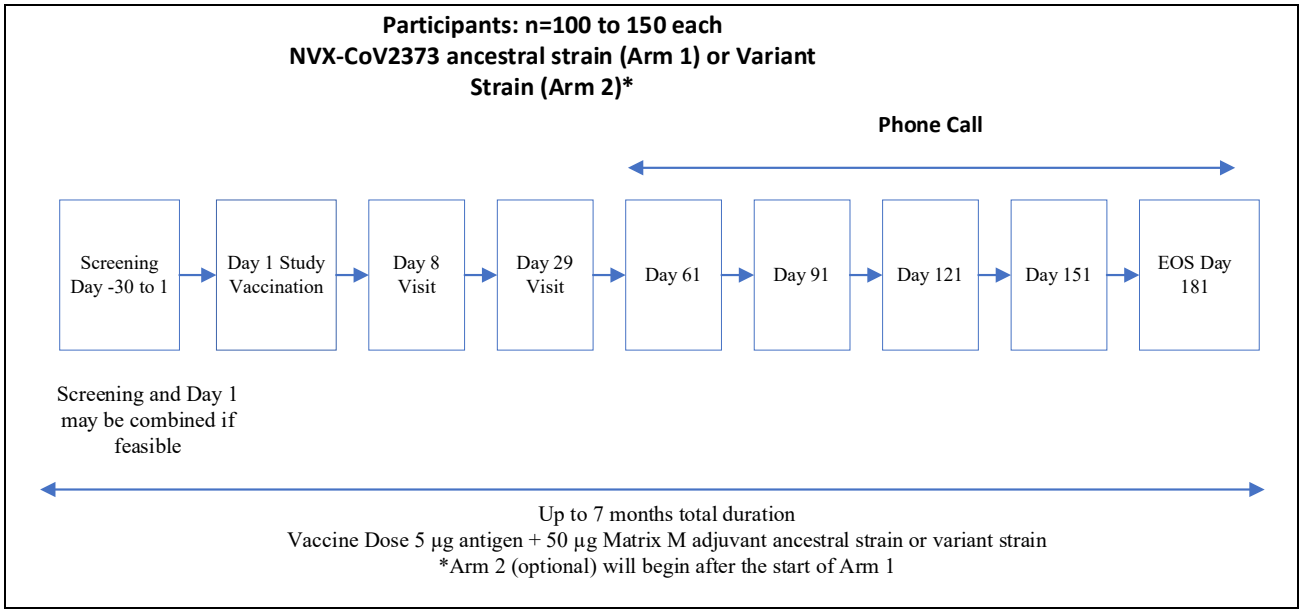
Vaccine	Age (years)*	Baseline Serostatus	Number of doses	Number of participants	Dose (antigen/ Matrix-M adjuvant)
Ancestral strain NVX-CoV2373	18 – 49	Previously vaccinated	1	100 – 150	5 µg / 50 µg
Updated Novavax COVID-19 Vaccine based on recent variant(s)	18 – 49	Previously vaccinated	1	100 – 150	5 µg / 50 µg

*Age at time of enrollment 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 (Figure 1).

Figure 1: Flow Diagram of Study 2019nCoV-312



1.2 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).

MN_{50} 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 MN_{50} GMR 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 2) is based on providing at least 90% power to conclude non-inferiority on Nab titers given the null hypothesis (Section 7.1) of $GMR_{312/307}$ defined as the ratio of GMT_{312} to $GMT_{307} \leq 0.67$. Here, GMT_{312} is Nab GMT at Day 29 from 2019nCoV-312 and GMT_{307} is Nab GMT at Day 29 from 2019nCoV-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 2: Summary of Sample Size

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

Note: GMR is defined as the ratio of Day 29 GMT in 2019nCoV-312 to Day 29 GMT in 2019nCoV-307; N is the count of participants.

1.3 Scope of the Analysis Plan

This statistical analysis plan (SAP) provides a detailed outline of the immunogenicity and safety analyses in accordance with Study Protocol 2019nCoV-312 Version 1.0, dated 10 February 2023 (Study 312 Protocol), and will address the analysis presentation of interim analysis (or called Day 29 primary analysis) review of all immunogenicity and safety data through Day 29. This SAP will also address the analysis presentation of final analysis review of all safety data through EoS.

Any deviations from this SAP will be described and justified in the Clinical Study Report (CSR).

All data analyses and generation of TLFs will be performed using SAS 9.4® or higher.

2 OBJECTIVES AND ENDPOINTS

An overview of all study objectives and endpoints in provided in Table 3.

Table 3: 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 2019nCoV-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 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 2019nCoV-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.

Table 3: Study 2019nCoV-312 Objectives and Endpoints

	Objectives	Endpoints
Secondary (cont.)	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 (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.

3 ANALYSIS SUBSETS

The following analysis sets are identified for analysis.

3.1 Selected Participants Analysis Set

The Selected Participants Analysis Set will include all participants who are enrolled, regardless of whether they 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.

3.2 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. Please note, the analysis per FAS will not be performed due to the change of enrollment procedure, that is, subjects to be dosed with ancestral strain NVX-CoV2373 are enrolled first and subjects to be dosed with updated Novavax COVID-19 Vaccine based on recent variant(s) are enrolled afterward.

3.3 Safety Analysis Set

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

3.4 Per-Protocol Analysis Set

The first Per-Protocol Analysis Set (PP1) will include all participants who receive the study vaccine according to the protocol with no receipt of another COVID vaccine (authorized or approved) after Day 1 vaccination, have serology results for baseline and Day 29 available after the vaccination, are PCR negative at baseline for SARS-CoV-2**,** do not report SARS-CoV-2 infection through Day 29 blood draw, and have no major protocol violations that are considered clinically relevant to impact immunogenicity response as determined by Novavax prior to database lock. This population will reflect the general population many of whom, three years into the pandemic, have experienced SARS-CoV-2 infection, and the immunogenicity measured after study vaccine may reflect “hybrid immunity”. Negative anti-NP result at baseline is not required. Participants with missing anti-NP at baseline will be included in the PP1.

The second Per-Protocol Analysis Set (PP2), intended to represent individuals who have not experienced natural SARS-CoV-2 infection, is defined similarly to PP1 except that it requires a negative baseline anti-N result. Participants with missing baseline anti-N results will be excluded from second Per-Protocol Analysis Set (PP2).

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

3.4.1 Anti-S Protein IgG Serology Subset

All participants in each PP Analysis Set who are tested for anti-S protein IgG antibodies using ELISA prior to study vaccination will be included in this subset.

3.4.2 Neutralization Assay Subset

All participants in each PP Analysis Set who are tested for neutralizing antibodies prior to study vaccination will be included in this subset.

3.4.3 hACE2 Receptor-Binding Inhibition Assay Subset

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

3.5 Discussion of Populations to be Used for Various Analyses

All selected participants will be used for subject disposition. Demographic data and other baseline data will be based on Safety Analysis Set and both PP Analysis Sets. Besides safety AE summaries, prior and concomitant medications, medical history, and protocol deviations, physical examination will be based on the Safety Analysis Set. Immunogenicity summaries and associated statistical analyses will be based primarily on both PP Analysis Sets (PP1 and PP2).

3.5.1 Protocol Deviations

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.

Some PDs may be determined programmatically through the course of the trial. Syneos ensures these are reconciled with manually determined PDs in Syneos's CTMS (clinical trial management system). Examples of programmatically determined PDs are provided in Table 4.

Table 4: Programmatically Determined Protocol Deviations

Inclusion/Exclusion Criteria Not Met
Missed Visit or Blood Draw
Out of Window Visit or Blood Draw
Trial Procedure Not Done

Review and categorization of protocol deviations will occur prospectively during the study prior to database freeze or lock(s). The PD listing collected by Syneos CTMS suitable for import for SAS will provide the category of protocol deviation and the corresponding description of each protocol deviation, with a flag to indicate if a deviation was recommended by Syneos to consider as major or minor.

3.5.2 Major Protocol Deviations Assessment

Protocol deviations deemed to indicate clear violations of GCP and/or subject consent; or to have a likely effect on the primary and secondary immunogenicity outcomes will exclude those participants from both PP analysis sets (PP1 and PP2). This determination will be made by the NOVAVAX Clinical Lead prior to database freeze or lock.

When interim analysis (Day 29 primary analysis) DB freezes or Day 181 final analysis DB locks, Syneos will assess protocol deviations and create a consensus final protocol deviations assessment file. NOVAVAX team will determine whether PDs are major and make the final decision of which participants will be excluded from the PP analysis based on the PD listing from Syneos.

In general, inclusion/exclusion criteria failure, receipt of prohibited therapies, receipt of another COVID vaccine (authorized or approved), missed blood draw and laboratory samples obtained sufficiently outside visit windows to likely impact the result will be deemed “major” deviations relevant for analysis. Criteria for this determination will be established prior to review of PDs. Any positive PCR or anti-NP result obtained at baseline Day 1 is not exclusionary and will not be considered a major PD.

4 PARTICIPANT DISPOSITION

The number of participants consented, enrolled, and vaccinated will be presented by the study vaccine group for all participants in the Selected Participants Analysis Set.

The number (percentage) of participants in the Selected Participants Analysis Set, Safety Analysis Set, and both PP Analysis Sets who have completed the study from Day 1 through Day 29 for the interim analysis (Day 29 primary analysis) and who have completed the study from Day 1 through EoS for the final analysis will be summarized by the study vaccine group.

The number (percentage) of participants in the Safety Analysis Set who discontinue the study prior to Day 29/EoS and the reason for study discontinuation (eg, AE, death, lost to follow-up, physician/investigator decision, sponsor decision, withdrawal of consent, etc.) 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. A listing of all screened participants who failed the inclusion/exclusion criteria will also be provided.

The number (percentage) of participants in the Safety Analysis Set with major protocol deviations recorded prior to Day 29/throughout the study will be summarized by the study vaccine group and protocol deviation category (according to the Protocol Deviations and Site Level Non-compliances provided by Syneos and confirmation by NOVAVAX). 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.

5 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Baseline demographic and background characteristics (eg, age at Day 1 vaccination, self-identified gender, race, ethnicity, height, weight, BMI, child-bearing potential and ECG) will be summarized by the study vaccine group on Safety Analysis Set, and both Per Protocol Sets (PP1 and PP2).

Descriptive statistics (total number of participants [n], mean and standard deviation (SD), median, minimum and maximum values) will be summarized for weight (kg) and height (cm), and derived BMI recorded at Study Day 1. Age (years) at the Day 1 vaccination will be calculated as the closest lower integer result of (Date of Study Day 1 – Date of Birth + 1) / 365.25 and will be summarized using the above descriptive statistics.

The number and percentage of participants for Gender (Male, Female, Other), Ethnicity (Hispanic or Latino, not Hispanic or Latino, not reported), Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White or Caucasian, Not Reported, Other), and BMI category will be summarized.

BMI categories are:

- Underweight: < 18.5
- Healthy: 18.5 – 24.9
- Overweight: 25.0 – 29.9
- Obese: ≥ 30.0

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.

Medical history will be coded using the 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.

Physical examination at screening will include height and weight, cervical and axillary lymph nodes, heart, and any other symptom-directed (targeted) examination. Symptom directed (targeted) examination will be performed at unscheduled visits. Diagnoses/abnormalities will be recorded by body system. Physical examination findings will be summarized by study vaccine group and by

body system. Abnormal results will also be summarized as clinically significant or not clinically significant.

The time between Day 1 vaccination dose in Day 307 and Day 1 vaccination dose in Study 312 may be summarized for the study vaccine group using descriptive statistics (ie, mean, median, standard deviation, minimum, maximum).

6 EXTENT OF EXPOSURE

6.1 Study Vaccine

Subject vaccination exposure will be summarized as the number and percentage of participants who received the study vaccine at Day 1 by the study vaccine group.

6.2 Prior and Concomitant Medication and Vaccination

Prior and concomitant medications include recent (≤ 90 days) and current medications, including non-COVID-19 vaccinations. All COVID-19 vaccines administered prior to screening will be recorded in the vaccine history eCRF. After Day 29, all COVID-19 vaccines, and only concomitant medications and other vaccines that have caused or are used to treat an AE will be recorded.

The number (percentage) of participants who record one or more prior/concomitant medications (including vaccines) recorded in the prior/concomitant medications eCRF will be summarized by the study vaccine group and preferred drug name as coded using the WHO drug dictionary for all participants in the Safety Analysis Set. Multiple occurrences of medication usage for a participant will be counted only once within an anatomical therapeutic chemical (ATC) term and standardized medication name.

A by-participant listing of treatment-emergent new concomitant medications (including vaccines) will be presented.

7 ANALYSES ADDRESSING PROTOCOL OBJECTIVES

7.1 Statistical Hypothesis

FoFor To evaluate the 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, two statistical hypotheses will be evaluated in the group receiving **ancestral strain NVX-CoV2373**.

- Non-inferiority of a second (or subsequent) booster dose of NVX-CoV2373, as measured by the lower-bound (LB) of the 95% confidence interval (CI) for $GMR_{312/307}$ defined as the ratio of Nab Geometric Mean Titer (GMT) **28 days after a second (or subsequent) booster dose** of NVX-CoV2373 in Study **2019nCoV-312** versus **28 days after a first booster dose** of NVX-CoV2373 in Study **2019nCoV-307** among the same participants being > 0.67. This is expressed statistically as:

  H_0: $GMR_{312/307} \leq 0.67$
  H_1: $GMR_{312/307} > 0.67$

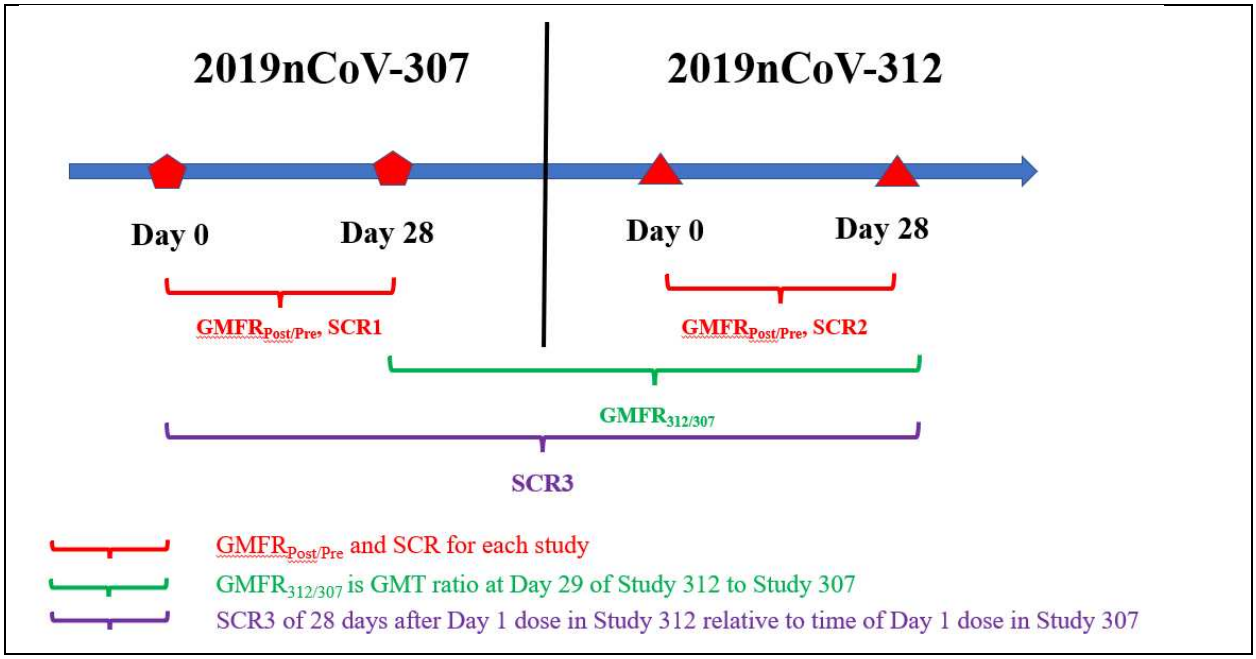
- Non-inferiority of a second (or subsequent) booster dose of NVX-CoV2373, as measured by the lower-bound (LB) of the 95% exact CI for the difference of proportion of participants with seroconversion (SCR) in Nab titers **28 days after a second (or subsequent) booster dose** of NVX-CoV2373 in Study **2019nCoV-312** relative to time of Day 1 dose in Study **2019nCoV-307** versus **28 days after a first booster dose** of NVX-CoV2373 in Study **2019nCoV-307** relative to time of Day 1 dose in Study **2019nCoV-307** among the same participants being > -10%. This is expressed statistically as:

  H_0: $SCR_{312} - SCR_{307} \leq -10\%$
  H_1: $SCR_{312} - SCR_{307} > -10\%$

Successful demonstration of non-inferiority of the booster dose requires lower-bound (LB) of the 95% confidence interval (CI) for $GMR_{312/307}$ defined as the ratio of Nab Geometric Mean Titer (GMT) **28 days after a second (or subsequent) booster dose** of NVX-CoV2373 in Study **2019nCoV-312** versus **28 days after a first booster dose** of NVX-CoV2373 in Study **2019nCoV-307** among the same participants being > 0.67 to meet the primary endpoint (Figure 2). If non-inferiority is demonstrated, successful demonstration of superiority being $GMR_{312/307}$ > 1.0 will meet the primary endpoint.

Successful demonstration of non-inferiority of the booster dose requires the lower-bound (LB) of the 95% exact CI for the difference of proportion of participants with seroconversion (SCR) in Nab titers **28 days after a second (or subsequent) booster dose** of NVX-CoV2373 in Study **2019nCoV-312** relative to time of Day 1 dose in Study **2019nCoV-307** versus **28 days after a first booster dose** of NVX-CoV2373 in Study **2019nCoV-307** relative to time of Day 1 dose in Study **2019nCoV-307** among the same participants being > -10% to meet the secondary endpoints.

Figure 2: Geometric Mean Titer and Seroconversion Rate Comparison between 2019nCoV-312 and Study 2019nCoV-307



7.2 Analysis of Primary/Secondary Endpoints of Immunogenicity

The immunogenicity analysis will be performed using the first PP Analysis Set (PP1) and the second PP Analysis Set (PP2). No missing data will be imputed. Titers/ELISA Units reported below the lower limit of quantification (LLOQ) will be set to half that limit (ie, if LLOQ=10, then 10/2 = 5) for use in computations.

7.2.1 Nab Titers for SARS-CoV-2

As the primary objectives of charactering Nab response 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 derived/calculated endpoints of Nab response for **the group receiving ancestral strain Novavax vaccine** will include:

- Nab GMT is calculated as the antilog of the mean of the log-transformed Nab titers. Nab GMT will be summarized by visit day (Days 1 and 29) along with the corresponding 2-sided 95% CIs, by exponentiating the corresponding log-transformed means and their 95% CIs.

- $GMFR_{Post/Pre}$ is calculated as the within-group ratio of post-vaccination Nab GMT at Day 29 to pre-vaccination Nab GMT at the baseline (Day 1).
  - $GMFR_{Post/Pre}$ will be calculated using this formula:

$$GMFR_{Post/Pre} = 10^{\left\{\frac{\sum_{i=1}^{n} \log_{10} v_{ij}/v_{ik}}{n}\right\}} = 10^{\frac{\{\sum_{i=1}^{n}(\log_{10} v_{ij} - \log_{10} v_{ik})\}}{n}}$$

where, for n participants, v_{ij} and v_{ik} are observed immunogenicity titers for subject i at time points j (post-vaccination at Day 29) and k (pre-vaccination at Day 0).

  - Below sample SAS code will be conducted using paired t distribution to estimate $GMFR_{Post/Pre}$ and corresponding 95% CIs.

```
proc means data=Nab_D1andD29_nonmissing n mean std t prt clm;
  var diff_aval;
  output out=paired N=n MEAN=mean STDERR=stderr STD=stddev
  LCLM=lclm UCLM=uclm prt=prt;
run;
```

- $GMR_{312/307}$ defined as the ratio of Nab Geometric Mean Titer (GMT) **28 days after a second (or subsequent) booster dose** of NVX-CoV2373 in Study **2019nCoV-312** versus **28 days after a first booster dose** of NVX-CoV2373 in Study **2019nCoV-307** among the same participants with the corresponding 95% CIs will be conducted using paired t distribution. Non-inferiority will be demonstrated if $GMR_{312/307}$ of Nab titers is higher than 0.67 and superiority will be demonstrated if $GMR_{312/307}$ of Nab titers is higher than 1.0 after non-inferiority is successfully demonstrated.
  - $GMR_{312/307}$ will be calculated using this formula:

$$GMR_{312/307} = 10^{\left\{\frac{\sum_{i=1}^{n} \log_{10} v_{ij}/v_{ik}}{n}\right\}} = 10^{\frac{\{\sum_{i=1}^{n}(\log_{10} v_{ij} - \log_{10} v_{ik})\}}{n}}$$

    where, for n subjects, v_{ij} and v_{ik} are observed immunogenicity titers for subject i at time points j (28 days after a second (or subsequent) booster dose of NVX-CoV2373 in Study 2019nCoV-312) and k (28 days after a first booster dose of NVX-CoV2373 in Study 2019nCoV-307).

As the 1st secondary objectives of charactering Nab response 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 derived/calculated endpoints of Nab response for **the group receiving ancestral strain Novavax vaccine** will include:

- SCR is defined as proportion of participants who achieve seroconversion ≥ 4-fold increase from baseline in Nab titers at Day 29 if the baseline value is equal to or above LLOQ or at least 4-fold fold rise from LLOQ if the baseline value is lower than LLOQ.

- SCR in Nab GMEUs with corresponding two-sided exact binomial 95% CIs will be calculated using the Clopper-Pearson method with the following sample SAS code:

```
proc freq data=Nab noprint;
   tables seroconvind / binomial(exact) alpha=.05;
   output out=out1 binomial;
run;
```

- Two-sided 95% CIs of the difference in SCRs in Nab titers **28 days after a second (or subsequent) booster dose** of NVX-CoV2373 in Study **2019nCoV-312** relative to time of Day 1 dose in Study **2019nCoV-307** versus **28 days after a first booster dose** of NVX-CoV2373 in Study **2019nCoV-307** relative to time of Day 1 dose in Study **2019nCoV-307** among the same participants will be based on the method of confidence interval for the difference in two correlated proportions by Tango (SAP Section 11.6). Non-inferiority will be demonstrated if the LB of the 95% exact CIs for the difference of SCRs ($SCR_{312} – SCR_{307}$) in Nab titers is higher than –10%.

As the 3rd secondary objectives of characterizing 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, the derived/calculated endpoints of Nab response for **the group receiving updated Novavax COVID-19 Vaccine based on recent variant(s)** will include Nab GMTs at Days 1 and 29, $GMFR_{Post/Pre}$ (Day 29 vs. Day 1), $GMR_{312/307}$, SCRs (Day 29 vs. Day 1), and difference in SCRs ($SCR_{312} – SCR_{307}$) in Nab titers to be calculated using the same calculations and comparison periods as noted above for **the group receiving ancestral strain Novavax vaccine**.

Above parameters based on the Pseudovirus-based Nab response per Wuhan strain from Study 2019nCoV-307 tested by Monogram will be presented together with the summary of Study 2019nCoV-312 to evaluate the primary endpoints of Nab response.

Since the Pseudovirus-based Nab response (Wuhan) at 4 different visits including the date of 1st booster dose (Day 1 in 2019nCoV-307), 28 days after 1st booster dose (Day 29 in 2019nCoV-307), date of 2nd booster dose (Day 1 in 2019nCoV-312) and 28 days after 2nd booster dose (Day 29 in 2019nCoV-312) were tested using the similar Pseudovirus Neutralization Assay by two different labs of Monogram and NVX CI, below conversions will be applied to the individual value in the unit of ID50 to the value in the standard unit of IU/mL.

2019nCoV-307 (Monogram): ID50 * 0.1458 = IU/mL

2019nCoV-312 (NVX CI): ID50 * 0.214 =IU/mL Pseudovirus-based Nab response (Omicron BA.5) of Study 2019nCoV-312 will be presented including GMT, $GMFR_{Post/Pre}$ and SCR.

7.2.2 ELISA (IgG) ELISA Units for SARS-CoV-2

As the 2nd secondary objectives of demonstrating 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, the derived/calculated endpoints of IgG response for **the group receiving ancestral strain Novavax vaccine** will include:

- IgG GMEU is calculated as the antilog of the mean of the log-transformed IgG GMEU. IgG GMEU will be summarized by visit day (Days 1 and 29) along with the corresponding 2-sided 95% CIs, by exponentiating the corresponding log-transformed means and their 95% CIs.
- $GMFR_{Post/Pre}$ is calculated as the within-group ratio of post-vaccination IgG GMEU at Day 29 to pre-vaccination IgG GMEU at the baseline (Day 1). Similar sample SAS code as Nab will be applied to estimate IgG $GMFR_{Post/Pre}$ and corresponding 95% CIs.
- $GMR_{312/307}$ of IgG GMEU **28 days after a second (or subsequent) booster dose** of NVX-CoV2373 in Study **2019nCoV-312** versus **28 days after a first booster dose** of NVX-CoV2373 in Study **2019nCoV-307** among the same participants with corresponding 95% CIs will be conducted using paired t distribution. Non-inferiority will be demonstrated if $GMR_{312/307}$ of IgG GMEU is higher than 0.67 and superiority will be demonstrated if $GMR_{312/307}$ of IgG GMEU is higher than 1.0 after non-inferiority is successfully demonstrated.
- SCR is defined as proportion of participants who achieve seroconversion ≥ 4-fold increase from baseline in IgG GMEUs at Day 29 if the baseline value is equal to or above LLOQ or at least 4-fold fold rise from LLOQ if the baseline value is lower than LLOQ. 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 in SCRs in IgG GMEU **28 days after a second (or subsequent) booster dose** of NVX-CoV2373 in Study **2019nCoV-312** relative to time of Day 1 dose in Study **2019nCoV-307** versus **28 days after a first booster dose** of NVX-CoV2373 in Study **2019nCoV-307** relative to time of Day 1 dose in Study **2019nCoV-307** among the same participants will be based on the method of confidence interval for the difference in two correlated proportions by Tango (SAP Section 11.6). Non-inferiority will be demonstrated if the LB of the 95% exact CIs for the difference of SCRs ($SCR_{312} - SCR_{307}$) in IgG GMEUs is higher than –10%.

As the 3rd secondary objectives of characterizing 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, the derived/calculated endpoints of IgG response for **the group receiving updated Novavax COVID-19 Vaccine based on recent variant(s)** will include IgG GMEU at Day 1 and Day 29, $GMFR_{Post/Pre}$ (Day 29 vs. Day 1), $GMR_{312/307}$, SCRs (Day 29 vs. Day 1), and difference in SCRs ($SCR_{312} - SCR_{307}$) in

IgG GMEU to be calculated using the same calculations and comparison periods as noted above for **the group receiving ancestral strain Novavax vaccine**.

Please note above parameters of IgG data (Wuhan) from both studies of Study 2019nCoV-307 and 2019nCoV-312 will be presented together and above parameters of IgG data (Omicron BA.5) from both studies will be presented together to evaluate the secondary endpoints.

7.2.3 hACE2 Receptor-binding Inhibition Titers for SARS-CoV-2

As the 4th secondary objectives of further characterizing antibody responses in a human angiotensin-converting enzyme 2 (hACE2) receptor binding inhibition assay to the SARS-CoV-2 ancestral strain spike protein, the derived/calculated endpoints of hACE2 response will include hACE2 GMTs at Day 1 and Day 29, $GMFR_{Post/Pre}$ (Day 29 vs. Day 1), $GMR_{312/307}$, SCRs (Day 29 vs. Day 1), and difference in SCRs ($SCR_{312} - SCR_{307}$) in hACE2 titers using the same calculations and comparison periods as noted above for neutralizing antibodies. Please note, SCR is defined as proportion of participants who achieve seroconversion ≥ 4-fold increase from baseline in hACE2 titers at Day 29 if the baseline value is equal to or above LLOQ or at least 4-fold fold rise from LLOQ if the baseline value is lower than LLOQ.

Please note above parameters of hACE2 data (Wuhan) from Study 2019nCoV-307 will be presented together with the summary of 2019nCoV-312; hACE2 data (Omicron BA.5) of Study 2019nCoV-312 will be summarized including GMT, $GMFR_{Post/Pre}$ and SCR.

7.3 Analyses of Secondary Endpoint of Safety

As the secondary objective of describing 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, safety data include Solicited AEs, unsolicited AEs through Day 29 after the vaccination dose, MAAEs and AESIs (including myocarditis and/or pericarditis) through Day 181 after the vaccine dose and SAEs Day 181 after the vaccine dose. All safety analyses will be descriptive and conducted using the Safety Analysis Set. Missing data will not be imputed.

7.3.1 Solicited Adverse Events

Solicited AEs for this study are pre-specified in Section 8 and Appendix 2 of the Study 312 Protocol, including both injection site reactions (ie, pain, tenderness, redness, and swelling) and systemic events (ie, fatigue, headache, myalgia, arthralgia, oral temperature [for assessment of fever], vomiting) that are reported within seven days following the Day 1 vaccination. These events are considered related to the test article and are collected using a severity rating of 0 (Normal), or 1, 2, or 3 (mild, moderate or severe, respectively), using the maximal severity observed for the specific symptom post-vaccination. Notable exceptions include oral temperature and events of injection site redness and swelling, which is collected as a continuous variable and that uses the grade ranges established in TGS (Table 10 in Appendix 3). Oral temperature (fever)

will be summarized by severity according to regulatory guidance, eg, Grade 0 (Normal) < 38.0ºC, Grade 1 (Mild) = 38.0 – 38.4ºC), Grade 2 (Moderate) = 38.5 – 38.9ºC, Grade 3 (Severe) > 39.0 – 40 ºC, Grade 4 (Potential Life Threatening) > 40. Redness/Swelling will be summarized by severity according to regulatory guidance, eg, Grade 0 (Normal) < 2.5 cm, Grade 1 (Mild) = 2.5 – 5 cm, Grade 2 (Moderate) = 5.1 – 10 cm, Grade 3 (Severe) > 10 cm. Extracts of solicited AEs of redness and swelling will be reviewed by the NVX clinical team and a final memo documenting the outcomes of the adjudication will be prepared by the NVX clinical team prior to database freeze (Day 29 primary analysis) or database lock (Final analysis). Any Grade 4 (Potential Life Threatening) solicited events will be provided to NVX Biostatistician team for analysis.

The number and percentage (with two-sided exact 95% CIs using the Clopper-Pearson method) of participants reporting solicited injection site and systemic AEs within the post-vaccination window (Days 1 – 7) by the verbatim terms, by severity (mild, moderate, severe, potentially life threatening) using the maximal severity observed for the specific symptom post-vaccination, or by day after vaccination and severity will be summarized for the study vaccine group. The number of participants with a solicited AE continuing beyond Day 7 will also be reported.

The duration of solicited local and systemic AEs within the 7 days after vaccination and beyond Day 7 will be summarized by the study vaccine group using several methods described below.

1. The number of days (count) that the reaction was reported within the 7-day reactogenicity period. For example, if fever was reported on Day 2, Day 3, and Day 5, then the count duration would be reported as 3 days.
2. The continuous duration of the event within the 7-day reactogenicity period. For example, if fever was reported on Day 2, Day 3, and Day 5, then the duration would be reported as 4 days using the date of Day 5 as ending date and date of Day 2 as the starting date of the event.
3. The continuous duration of the event including continuing reactions past the 7-day reactogenicity period. For example, if a Fever was reported on Day 3, Day 4, Day 6, and in a linked unsolicited AE with an end date of Day 8, then the duration would be reported as 6 days using the date of Day 3 as the starting date of the event.

The following summaries of all solicited AEs will be presented by the study vaccine group as the part of safety stated as the secondary endpoints:

- All local/systemic reactogenicity AEs by the verbatim terms within the post-vaccination window (Days 1 – 7)
- All local/systemic reactogenicity AEs by severity within the post-vaccination window (Days 1 – 7)
- All local/systemic reactogenicity AEs by the verbatim terms beyond 7 days following the study vaccine

- All local/systemic reactogenicity AEs by severity beyond 7 days following the study vaccine
- Duration of solicited TEAEs within the post-vaccination window (Days 1 – 7)
- Duration of all solicited TEAEs after Day 1
- Listings of participants with local/systemic reactogenicity AEs

7.3.2 Unsolicited Adverse Events

A 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. AESIs include PIMMCs, myocarditis and/or pericarditis (Table 11 in Appendix 4), and complications specific to COVID-19 (Table 9 in Appendix 2). SAE is an event considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the outcomes listed in Section 8.1 of the Study 312 Protocol.

Unsolicited MAAEs through Day 29, and MAAEs attributed to study vaccine/AESIs/SAEs throughout the study will be summarized by the study vaccine group and by SOC/PT using the latest version of MedDRA, as well as by severity (Mild, Moderate, Severe) and relationship (not related, related) 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 through Day 29, MAAEs attributed to study vaccine after Day 29 until EoS, AESIs and SAEs throughout the study will be summarized and their corresponding by-participant listings will also be provided.

The following summaries of all unsolicited AEs will be presented by the study vaccine group as the part of safety stated as the secondary endpoints:

- Overall summary of all unsolicited TEAEs (Days 1 – 29)
- Summary of all unsolicited TEAEs by MedDRA SOC/PT and severity (Days 1 – 29)
- Summary of all unsolicited TEAEs by MedDRA SOC/PT and relationship to the study vaccine (Days 1 – 29)
- Summary of MAAEs by MedDRA SOC/PT and severity (Days 1 – 29)
- Summary of MAAEs by MedDRA SOC/PT and relationship to the study vaccine (Days 1 – 29)

- Summary of MAAEs attributed to study vaccine by MedDRA SOC/PT and severity (Days 1 – 29) and (Days 1 – 181)
- Summary of AESIs (including PIMMCs, myocarditis or pericarditis, and complications to COVID-19) by MedDRA SOC/PT and severity (Days 1 – 29) and (Days 1 – 181)
- Summary of AESIs (including PIMMCs, myocarditis or pericarditis, and complications to COVID-19) by MedDRA SOC/PT and relationship to study vaccine (Days 1 – 29) and (Days 1 – 181)
- Summary of SAE by MedDRA SOC/PT and severity (Days 1 – 29) and (Days 1 – 181)
- Summary of SAE by MedDRA SOC/PT and relationship to study vaccine (Days 1 – 29) and (Days 1 – 181)
- Duration of MAAEs (Days 1 – 29)
- Duration of MAAEs attributed to study vaccine (Days 1 – 29) and (Days 1 – 181)
- Duration of AESIs (Days 1 – 29) and (Days 1 – 181)
- Summary of unsolicited AEs leading to the discontinuation of study (Days 1 – 29) and (Days 1 – 181)
- Summary of SAEs leading to the discontinuation of study (Days 1 – 29) and (Days 1 – 181)
- Listings of all unsolicited AEs including MAAEs, AESIs (including PIMMCs, myocarditis or pericarditis and complications to COVID-19) and SAEs

7.4 Analysis of Exploratory Endpoints

The same statistical methods applied for the analysis of IgG, Nab, and hACE2 may also be applied to best characterize the immune response for future vaccine development needs, including testing against emerging variants of SARS-CoV-2 to evaluate immune responses developed based on the assays used as the exploratory endpoints.

8 ADDITIONAL ANALYSES

8.1 Vital Signs

Vital sign measurements at screening (if not performed on the same day as screening, VS is to be performed prior to study vaccination) including respiratory rate, blood pressure, pulse rate, and temperature (oral or via forehead/ear reader) will be summarized as continuous variables. Descriptive statistics for vital sign results at screening will be presented by the study vaccine group for all participants in the Safety Analysis Set, including means and SDs, median, minimum, and maximum. A by-participant listing of vital signs will be provided.

8.2 Physical Examinations

Physical examination at screening (if not performed on the same day as screening, PE is to be performed prior to study vaccination) includes height and weight, cervical and axillary lymph nodes, heart, and any other symptom-directed examination.

Symptom-directed (targeted) physical examination performed at screening and unscheduled visits will be summarized by study vaccine group and by body system. For each body system examined, the number and percentage of participants with normal/abnormal results will be reported. The calculation of abnormal results will also be broken out by whether the abnormal result was considered clinically significant or not.

9 CONDUCT OF ANALYSES

The first interim analysis (or called 1st Day 29 primary analysis) will be conducted when all available immunogenicity data (IgG, Nab, and hACE2) and safety data for **the group receiving ancestral strain NVX-CoV2373** through Day 29 have been entered, reviewed, and all queries related to the data have been addressed.

The secondary interim analysis (or called 2nd Day 29 primary analysis) will be performed when all available immunogenicity data (IgG, Nab, and hACE2) and safety data for **the group receiving updated Novavax COVID-19 Vaccine based on recent variant(s)** through Day 29 have been entered, reviewed, and all queries related to the data have been addressed.

The two interim analysis (both Day 29 primary analysis) may be combined depending on the processing of enrollment of participants in the group receiving **ancestral strain NVX-CoV2373** and participants in the group receiving **updated Novavax COVID-19 Vaccine based on recent variant(s)**.

Final analysis will be conducted when all available safety data throughout the study (from Day 1 through EoS) have been entered, reviewed, and all queries related to the data have been addressed.

10 COMPUTER METHODS

Statistical analyses will be performed using SAS® version 9.4 or higher in a Windows environment.

11 DATA HANDLING CONVENTIONS

All output will be incorporated into Microsoft Word or Excel files, or Adobe Acrobat PDF files, sorted and labeled according to the International Conference on Harmonisation (ICH) recommendations, and formatted to the appropriate page size(s).

Tabulations will be produced for appropriate demographic, baseline, and safety parameters. For categorical variables, summary tabulations of the number and percentage of participants within each category (with a category for missing data) of the parameter will be presented. For continuous variables, the number of participants, mean and standard deviation (SD), median, minimum, and maximum values will be presented.

All references to analysis of GMT/GMEU will be interpreted as analysis of the $\log_{10}$ of titer values or ELISA Units.

The individual immunogenicity (Nab) titer values, IgG ELISA Units and hACE2 receptor-binding inhibition titer values recorded as below the LLOQ of the assay will be set to half LLOQ for the purposes of GMT/GMEU analyses. The LLOQ values will be provided by corresponding labs.

Medical history and AEs will be coded using MedDRA Version 25.0.

Each parameter will be reported with the below defined decimal numbers in Table 5.

Table 5: Decimal Numbers for Parameters

Parameter	Number of Decimal
Number of participants (eg, N, N1, N2, n)	0
Percentage (%)	1
Mean	1 more decimal than raw data
Standard Deviation (SD)	1 more decimal than mean
Median, Min, Max	as same decimal as raw data
GMT, $GMFR_{Post/Pre}$, $GMR_{312/307}$, their corresponding 95% CIs	1
GMEU, $GMFR_{Post/Pre}$, $GMR_{312/307}$, their corresponding 95% CIs	1
SCR (%), their corresponding 95% CIs	1

11.1 Baseline Definitions

For all analyses, baseline is defined as the last non-missing measurement prior to the first administration of the study material. For immunogenicity analysis, baseline will be the result from the sample drawn on the day of vaccination (Day 1).

11.2 Adjustments for Covariates

Not applicable.

11.3 Multiple Comparisons/Multiplicity

Not applicable.

11.4 Withdrawals, Dropouts, and Loss to Follow-up

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

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 first 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.

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

11.5 Missing, Unused, and Spurious Data

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.

When tabulating AE and Concomitant Medications (exclusive of vaccinations prior to Dose 1) data, partial dates of event onset will be handled as follows:

- If the day of the month is missing, the onset date will be assumed to be the date of the Day 1 vaccination or first of the month, whichever is later, in order to conservatively report the event as treatment-emergent.
- If the onset day and month are both missing, the event onset will be coded to the date of the Day 1 vaccination or 1st January of the year, whichever is later, in order to conservatively report the event as treatment-emergent.

- A completely missing onset date will be coded as the date of the Day 1 vaccination, unless the end date suggests it could have started prior to this in which case impute the 1st January of the same year as the end date.
- No imputations will be made to event ending dates.
- When imputing a start date ensure that the new imputed date is prior to the end date of the AE or medication.

When tabulating Medical History or Previous Vaccination data, partial start dates of event will be handled as follows:

- For start date with a missing day and/or month, impute a missing day as the first of the month, and a missing month as January. The resulting date should be prior to the Day 1 vaccination and before the end date (full or partial date). A partial start date with an entirely missing ending date should result in a query to the site.
- For start date with a missing year, impute the year to be year of the ending date if it exists. Otherwise, the missing start date will be kept as missing.

For tabulations of AE, a top-level summary will be generated to report treatment-related AEs according to two conventions:

- No imputation of missing relationship to test article
- Consider the event to be treatment-related to test article.

Similarly, the top-level summary will report severe AEs according to two conventions:

- No imputation of missing severity
- Consider the event to be severe

Detailed presentation of AE data by SOC and preferred terms will be generated without first imputing missing relationship nor severity. As with missing dates, queries to the site should be undertaken before employing the reporting conventions described above.

11.6 Tango Confidence Interval

Two proportions from the same sample of observations or from matched-pair samples are correlated. McNemar's test (McNemar, 1947) is commonly conducted to test the equivalence of two correlated proportions (Table 6).

Table 6: Continency Table of Seroconversion Rate

		2019nCoV-312		
		SCR (Yes)	**SCR (No)**	**Total**
2019nCoV-307	SCR (Yes)	a (π_{11})	b (π_{12})	a + b (π_{1+})
	SCR (No)	c (π_{21})	d (π_{22})	c + d (π_{2+})
	Total	a + c (π_{+1})	b + d (π_{+2})	n

Testing the null hypothesis π_{1+} - π_{+1} = 0 is equivalent to testing π_{12} - π_{21} = 0. Given the null hypothesis, the McNemar's test statistic (Chi-squared) can be computed as follows:

$$\chi 2 = (b-c)^2/(b+c)$$

where

b is the frequency of participants who has seroconversion rate before booster dose but don't have seroconversion rate after booster dose, and

c is the frequency of participants who don't has seroconversion rate before booster dose but have seroconversion rate after booster dose

Under the null hypothesis, the McNemar's statistic follows an asymptotic chi-square distribution with one degree of freedom when b + c is greater than 10.

The confidence interval for the difference in two correlated proportions ($\lambda = \pi_{1+} - \pi_{+1} = \pi_{12} - \pi_{21}$) developed by Tango is estimated by solving the following two equations iteratively until the change in estimation is infinitesimal below the predetermined cutoff.

$$\frac{b-c-n\lambda}{\sqrt{n(2\hat{\pi}_{21}+\lambda(1-\lambda))}} = \pm z_{\alpha/2}$$

Where

λ is the difference between two correlated proportions, and

$\hat{\pi}_{21}$ is estimated as

$$\hat{\pi}_{21} = \frac{\sqrt{(B^2-4AC)}-B}{2A}$$

Where

$A = 2n$

$B = -b - c + (2n - b + c)\lambda$, and

$C = -c\lambda(1-\lambda)$

Although the computational procedures for Tango's CI are more complex, the upper and lower limits are easily found through the Secant method with empirically good coverage probabilities (Newcombe, R. G. 1998) and can be applied to small samples with off-diagonal zero cells Tango, T. 1998).

12 REFERENCES

Study 2019nCoV-312 protocol

Version 2.0 (Amendment 1.0) dated Feb.23, 2023

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13 APPENDICES

13.1 Appendix 1: Schedule of Events

Table 7: 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]							

Table 7: 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**
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]
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 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 SAP Appendix 4 (Table 11) for symptoms of myocarditis or pericarditis and Study 312 Protocol 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 SAP Appendix 4 (Table 11) for symptoms of myocarditis or pericarditis and Study 312 Protocol Table 4 for instructions for follow-up.

[12] EOS form will be completed for all participants, including participants who are terminated early.

13.2 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 8). 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 8: 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

Table 8: Potential Immune-Mediated Medical Conditions

Categories	Diagnoses (as MedDRA Preferred Terms)
Skin Disorders	Alopecia areata, psoriasis, vitiligo, Raynaud's phenomenon, erythema nodosum, autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis), cutaneous lupus erythematosus, morphoea, lichen planus, Stevens-Johnson syndrome, 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 thyroiditisa, diabetes mellitus type 1, Addison's disease.
Other Disorders:	Goodpasture syndrome, idiopathic pulmonary fibrosis, pernicious anemia, sarcoidosis.

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

Source: DaSilva 2013

Complications specific to COVID-19 are listed below (Table 9). The list is not intended to be exhaustive, nor does it exclude the possibility that other diagnoses may be AESI.

Table 9: Adverse Events Representing Complications Specific to of 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).

13.3 Appendix 3: Toxicity Grading Scale for Clinical Abnormalities, (local and general systemic reactogenicity, clinical laboratory, and vital signs)

Table 10: Modified FDA Toxicity Grading Scale for Clinical Abnormalities (Local and General Systemic Reactogenicity)

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

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

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

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

Source: FDA 2007

13.4 Appendix 4: 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 in Study 312 Protocol]) within 4 weeks after vaccination should be evaluated as soon as possible by a physician who should initiate a diagnostic work up including, but not limited to, laboratory tests and initial cardiac evaluation. If probable or confirmed myocarditis and/or pericarditis is diagnosed after the initial evaluation, all efforts will be made to route the participants to be followed up preferentially by a cardiologist or pediatric cardiologist (as applicable) who should complete the initial evaluation and manage cases following current practice guidelines (eg, AHA or other national/local guidelines); this might include performing functional cardiac evaluation and follow up of the case until resolution (see Table 4 in Study 312 Protocol). A Central Cardiac Adjudication Committee has been established to adjudicate probable myocarditis and/or pericarditis cases in the clinical development plan of NVX-CoV2373. Outcomes of the adjudications will be communicated to the SMC (when applicable) and to the Sponsor.

All myocarditis and/or pericarditis signs and symptoms, as well as all clinical evaluations, will be considered part of the study record and should be documented in the relevant eCRF pages. Participants with confirmed myocarditis or pericarditis will be followed-up to document resolution of symptoms and/or abnormal test findings (Table 11).

Table 11: Case Definitions of Probable and Confirmed Myocarditis, Pericarditis, and Myopericarditis

Condition	CDC Definition
Acute myocarditis	**PROBABLE**: Presence of ≥ 1 new or worsening of the following clinical symptoms:[1] • Chest pain, pressure, or discomfort • Dyspnea, shortness of breath, or pain with breathing • Palpitations • Syncope AND ≥ 1 new finding of • Troponin level above upper limit of normal (any type of troponin) • Abnormal ECG or rhythm monitoring findings consistent with myocarditis [2] • Abnormal cardiac function or wall motion abnormalities on echocardiogram • cMRI findings consistent with myocarditis [3] AND • No other identifiable cause of the symptoms and findings

Table 11: Case Definitions of Probable and Confirmed Myocarditis, Pericarditis, and Myopericarditis

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

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

[1] Persons who lack the listed symptoms but who meet other criteria may be classified as subclinical myocarditis (probable or confirmed).

[2] Using the Dallas criteria [Aretz 1987]

. Autopsy cases may be classified as confirmed clinical myocarditis on the basis of meeting histopathologic criteria if no other identifiable cause.

[3] To meet the ECG or rhythm monitoring criterion, a probable case must include at least one of 1) ST-segment or T-wave abnormalities; 2) Paroxysmal or sustained atrial, supraventricular, or ventricular arrhythmias; or 3) AV nodal conduction delays or intraventricular conduction defects.

[4] Using either the original or the revised Lake Louise criteria [Ferreira 2018].

[5] Based on the 2015 ESC Guidelines for the diagnosis and management of pericardial diseases [Adler 2015].

[6] Typically described as pain made worse by lying down, deep inspiration, or cough, and relieved by sitting up or leaning forward, although other types of chest pain might occur.

Adapted from Gargano 2021