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A RANDOMIZED, OBSERVER-BLINDED, PHASE 3 STUDY TO COMPARE THE IMMUNOGENICITY AND SAFETY OF 3 LOTS OF NVX-COV2373 IN ADULTS

Novavax Protocol Number: **2019nCoV-307**

STATISTICAL ANALYSIS PLAN (SAP) for Final Analysis of Immunogenicity and Safety Data

SAP Version and Date: Version 2.0 – 29 July 2022

Investigational Product: NVX-CoV2373 (5 µg): Prototype SARS-CoV-2 rS.

APPROVAL SIGNATURE PAGE

Protocol Number:	2019nCoV-307
Protocol Version and Date:	Version 5.0/Amendment 4 20 July 2022
Protocol Title:	A Randomized, Observer-Blinded, Phase 3 Study to Compare the Immunogenicity and Safety of 3 Lots of NVX-CoV2373 in Adults
SAP Version and Date:	Version 2.0 – 29 July 2022

☐ Original Statistical Analysis Plan

☒ Amended Statistical Analysis Plan

SAP Originated By: [redacted] Project Statistician Date

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

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Date

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Date

Signed Electronically

[redacted]

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LIST OF ABBREVIATIONS

Abbreviation or Term	Definition
AE	Adverse event
AESI	Adverse event of special interest
ANCOVA	Analysis of covariance
BMI	Body mass index
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CRO	Clinical research organization
CSR	Clinical Study Report
CTMS	Clinical trial management system (Syneos)
DAIDS	Division of AIDS, NIAID, NIH
DoE	Design of Experiments
eCRF	Electronic case report form
ECG	Electrocardiogram
EDC	Electronic data capture
eDiary	Electronic participant-reported outcome diary application
ELISA	Enzyme-linked immunosorbent assay
EoS	End of study
FDA	United States Food and Drug Administration
HEENT	Head nose ears and throat
GCP	Good Clinical Practice
GMEU	Geometric mean ELISA Unit
GMEUR	Geometric mean ELISA unit ratio (between groups)
GMFR	Geometric mean fold rise (within group)
GMT	Geometric mean titer
GMTR	Geometric mean titer ratio (between groups)
HA	Hemagglutinin
hACE2	Human angiotensin-converting enzyme 2
ICF	Informed consent form
ICH	International Council for Harmonisation
IgG	Immunoglobulin G
IM	Intramuscular
IWRS	Interactive Web Response System
LLOQ	Lower limit of quantification

Abbreviation or Term	Definition
MAAE	Medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MN	Microneutralization (assay)
MN_{50}	Microneutralization assay with an inhibitory concentration of 50%
NVX-CoV2373	SARS-CoV-2 rS with Matrix-M adjuvant
PCR	Polymerase chain reaction
PIMMC	Potential immune-mediated medical conditions
PP	Per-Protocol
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SARS-CoV-2 rS	Severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine
SCR	Seroconversion rate
SOC	System organ class
SOE	Schedule of Events
TEAE	Treatment-emergent adverse event
WHO	World Health Organization

1 INTRODUCTION

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

NVX-CoV2373 is the prototype SARS-CoV-2 rS nanoparticle vaccine construct adjuvanted with Matrix-M™ adjuvant that is intended to be used for the active immunization for the prevention of mild, moderate, and severe COVID-19 caused by SARS-CoV-2 in adults 18 years of age and older. The investigational products used in this study are manufactured by Serum Institute of India (SII) through a partnership with Novavax.

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

1.1 Study Design

This is a randomized, Phase 3 study comparing the immunogenicity and safety of 3 different lots of Novavax vaccine with Matrix-M™ adjuvant (NVX-CoV2373). The study will enroll approximately 900 previously vaccinated adults 18 to 49 years of age, inclusive.

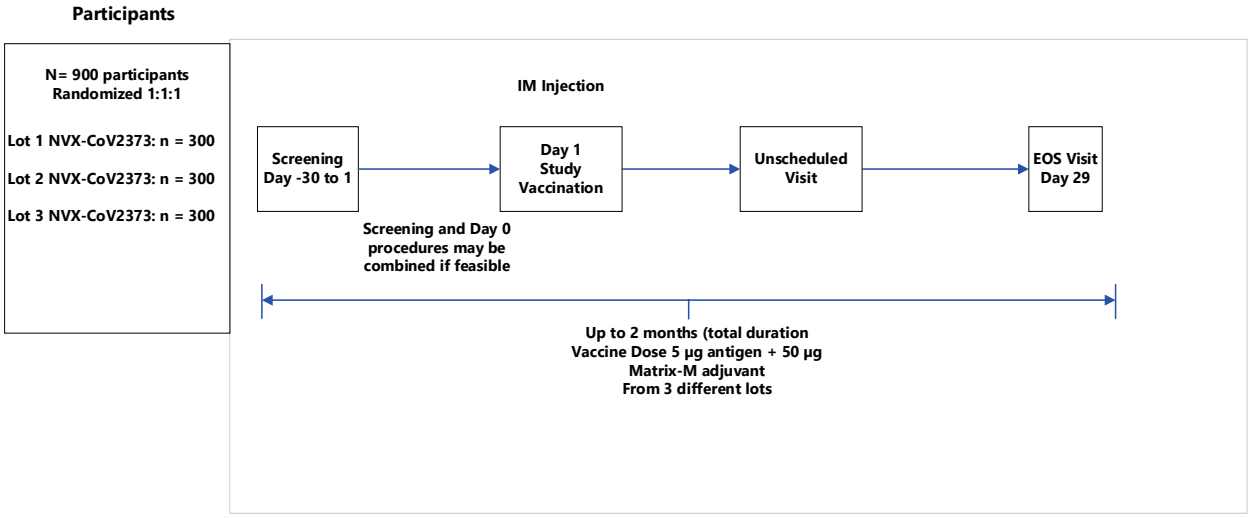
Approximately 1200 potential participants will be screened at baseline with the goal of enrolling approximately 900 previously vaccinated participants. Participants will be randomized 1:1:1 to receive 1 dose of the vaccine from 1 of 3 different lots, given on Day 1, at a dose level of 5 µg of antigen with 50 µg of Matrix M adjuvant as per the Study Vaccinations (Table 1).

Table 1 Study Vaccinations

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

All participants will remain on study for immunogenicity and safety data collection through 28 days following the vaccination (Figure 1, Appendix 1).

Figure 1 Flow Diagram for 2019nCoV-307



Abbreviations: EOS=end of study

1.2 Sample Size Rationale

The sample size and power are driven by the primary endpoint (ie, lot consistency in terms of immunogenicity measured by IgG response at Day 29). Based on IgG data from Novavax's study 2019nCoV-101 Part 2, previously vaccinated participants in the 18-49-year-old age group who received the SARS-CoV-2 rS vaccine, exhibited an 80% confidence upper bound of Day 29 IgG SD in log10 scale of 0.39. The immunogenic performance of the released lots should be approximately the same; ie, the lot-to-lot GMEU ratio should approximate 1.0. Under any manufacturing practices, between-lot variation exists and is considered normal. Assuming 10% variation (lot-to-lot GMEU ratio is 1.1), an evaluable sample size of 248 subjects for each lot in the per-protocol population will be required to achieve 97% power to demonstrate the lot-to-lot equivalence and provide the overall power of ~90% for all three lot-to-lot equivalence tests (Lot 1 vs. Lot 2, Lot 1 vs. Lot 3, and Lot 2 vs. Lot 3). Accounting for a ~5% dropout rate, a total enrollment sample size of 300 participants will provide 262 participants per lot.

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

1.3 Randomization Strategy and Procedure

An Interactive Web Response System (IWRS) will be responsible for the allocation of randomization numbers to individual participants. Participants will be randomized in a 1:1:1 ratio to receive one of 3 lots of the study vaccine.

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

1.4 Blinding

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

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

An IWRS will be responsible for the allocation of randomization numbers to individual participants. Randomization will take place at baseline after confirmation that the participant meets the inclusion/exclusion criteria.

1.5 Scope of the Analysis Plan

This statistical analysis plan (SAP) provides a detailed outline of the safety and immunogenicity analyses in accordance with Study Protocol 2019nCoV-307 Version 5.0/Amendment 4, dated 20 July 2022, and will address the analysis presentation of final EoS analysis review of all data through Day 29 for the completed study.

Final EoS analysis review will be conducted when all available safety and immunogenicity data (IgG, MN_{50}, and hACE2) through Day 29 have been entered, reviewed, and all queries related to the data have been addressed.

2 OBJECTIVES AND ENDPOINTS

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

Table 1 Study 2019nCoV-307 Objectives and Endpoints

	Objectives	Endpoints
Primary	To demonstrate the equivalence of 3 different vaccine lots based on IgG responses.	IgG geometric mean ELISA unit concentrations (GMEU/mL) to the SARS-CoV-2 spike protein at Day 29 in each treatment arm; Equivalence will be demonstrated if the 95% CIs of GMEUs for all pairs of lots are within the pre-specified equivalence range of 0.67 to 1.5.

Table 1 Study 2019nCoV-307 Objectives and Endpoints

	Objectives	Endpoints
Secondary	To characterize the IgG antibody responses to 3 different lots of NVX-CoV2373	Proportion of participants in each treatment arm who achieve seroconversion (≥ 4-fold increase from baseline) in IgG concentrations to the SARS-CoV-2 spike protein at Day 29.
	To characterize the neutralizing antibody responses to 3 different lots of NVX-CoV2373.	• MN_{50} geometric mean titers to the SARS-CoV-2 spike protein at Day 29 in each treatment arm. • Proportion of participants in each treatment arm who achieve seroconversion (≥ 4-fold increase from baseline) in MN_{50} titers to the SARS-CoV-2 spike protein at Day 29.
	To characterize antibody responses in a human angiotensin-converting enzyme 2 (hACE2) receptor binding inhibition assay to the SARS-CoV-2 spike protein in participants vaccinated with 3 different lots of NVX-CoV2373.	• hACE2 inhibition assay titers (geometric mean titer [GMTs]) at Day 29 in each treatment arm • Proportion of participants in each treatment arm who achieve seroconversion (≥ 4-fold increase from baseline) in hACE2 titers concentrations to the SARS-CoV-2 spike protein at Day 29.
	To compare the overall safety of 3 different lots of NVX-CoV2373	• Incidence, duration, severity, and relationship of MAAEs and AESIs (including myocarditis and/or pericarditis) through Day 29 (ie, 28 days after vaccine dose). • Incidence and relationship of SAEs throughout the study.
Exploratory	To utilize additional assays (current or to be developed) to best characterize the immune response for future vaccine development needs.	Additional endpoints to compare immune responses may be developed based on the assays used.

3 ANALYSIS SUBSETS

The following analysis sets are identified for analysis.

3.1 Randomized Participants Analysis Set

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

3.2 Full Analysis Set

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

3.3 Safety Analysis Set

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

3.4 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 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 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.

3.4.2 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.

3.4.3 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.

3.5 Discussion of Populations to be Used for Various Analyses

Demographic data, baseline data, and safety AE summaries will be based on the Safety Analysis Set. All participants randomized will be used for subject disposition. Immunogenicity summaries and associated statistical analyses will be based primarily on the PP Analysis Set and may also be analyzed with the FAS.

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, if 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 3.

Table 3 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
Randomization Error, i.e. subject administered IP not per assignment by IRT

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 considered major and resulted in the exclusion of the participant from the PP analysis set.

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 the PP analysis set. Prior to unblinding, 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, and far away from visit window will be deemed "major" deviations relevant for analysis.

4 SUBJECT DISPOSITION

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

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

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

The number (percentage) of participants in the Safety Analysis Set with major protocol deviations recorded throughout the study will be summarized by the study vaccine group and protocol deviation category (according to the Protocol Deviations and Site Level Non-compliances provided by Syneos). 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, gender, race, ethnicity, height, weight, BMI, child-bearing potential and ECG) will be summarized overall and by the study vaccine group on the FAS, Safety Analysis Set, and Per Protocol Set.

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

Baseline ECGs will be read and interpreted by a Central Cardiac Adjudication Committee only as a comparison with new ECG(s) in the event that the participant experiences a cardiac event during the 28 days following vaccine administration that requires review by the Cardiac

Adjudication Committee. Baseline ECGs will be summarized by the study vaccine group and by normal/abnormal. A by-participant listing of baseline ECGs will be provided.

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 diagnoses/abnormalities will be recorded by body system. Physical examination findings will be summarized by study vaccine group and by body system.

Participants will also be summarized by the study vaccine group and the name of previous COVID-19 vaccination (Novavax, Moderna, Pfizer, Johnson&Johnson, Other). In addition, the time between first dose of previous COVID-19 vaccination and Day 1 vaccination dose may be summarized by the study vaccine group using descriptive statistics (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 medications include recent (≤ 90 days) and current medications and non-Covid-19 vaccinations. Concomitant medications will include all medications (including vaccines) taken by the participant from the time of signing the ICF through EOS (or through the early termination visit if prior to that time).

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 overall and 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 Analysis of Primary/Secondary Endpoints of Immunogenicity

The immunogenicity analysis will be performed using the PP Analysis Set. The FAS may be used to provide a supportive analysis if a large number of participants are excluded from the PP analysis. 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.

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

As the primary objectives, IgG GMEUs (EU/mL) to the SARS-CoV-2 spike protein in previously vaccinated participants 18 to 49 years of age, the derived/calculated endpoints of IgG response will include:

- IgG GMEU is calculated as the antilog of the mean of the log-transformed IgG GMEU at Days 1 and 29. IgG GMEU will be summarized by the study vaccine group and visit day 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 ratio of post-vaccination IgG GMEU at Day 29 to pre-vaccination IgG GMEU at the baseline (Day 1).
    - IgG $GMFR_{Post/Pre}$ for each study vaccine group will be conducted using paired t distribution. A sample SAS code is given below to estimate IgG $GMFR_{Post/Pre}$ and corresponding 95% CIs.

```
proc means data=IgG_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;
```

- IgG GMEUR between any two of study vaccine groups at Day 29 and the two-sided 95% CIs will be computed using analysis of covariance (ANCOVA), with the study vaccine group as the fixed effect and IgG ELISA unit at Day 1 (adjusted for intergroup variation in baseline [pre-vaccination] IgG ELISA unit) as the covariate under two-sided type I error rate of 0.05. No type I error rate adjustments will be made. The mean difference of all lots paired comparisons with their corresponding CI limits will then be exponentiated to obtain IgG GMEUR and the corresponding 95% CIs.
    - Sample SAS code for GMEUR for all pairwise comparisons (Group 1 vs. Group 2, Group 1 vs. Group 3, and Group 2 vs. Group 3) is given below:

```
proc mixed data=IgG;
      class Group;
      model log(IgG) = log(IgG_D0) Group;
      lsmeans Lot/cl diff e alpha=0.05;
run;
```

As the 1st secondary objectives, IgG GMEUs (EU/mL) to the SARS-CoV-2 spike protein in previously vaccinated participants 18 to 49 years of age, the derived/calculated endpoints of IgG response will include:

- SCR is defined as proportion of participants who achieve seroconversion ≥ 4-fold increase from baseline in IgG GMEUs at Day 29. SCR in IgG 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=IgG noprint;
      by Group;
      tables seroconvind / binomial(exact) alpha=.05;
      output out=out1 binomial;
run;
```

- Two-sided 95% CIs of the difference of SCRs in IgG GMEUs for all pairwise comparisons will be based on the Miettinen and Nurminen method with the following sample SAS code:

```
proc freq data=IgG;
      tables Group*scr / missing riskdiff (cl=MN);
run;
```

7.1.2 MN_{50} Titers for SARS-CoV-2

As the 2nd secondary objectives, neutralizing antibody response to the SARS-CoV-2 spike protein in previously vaccinated participants 18 to 49 years of age, the derived/calculated endpoints of MN_{50} response will include:

- MN_{50} GMT is calculated as the antilog of the mean of the log-transformed MN_{50} titers at Days 1 and 29. MN50 GMT will be summarized by the study vaccine group and visit day 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 ratio of post-vaccination MN50 GMT at Day 29 to pre-vaccination MN_{50} GMT at the baseline (Day 1). Similar sample SAS code as IgG will be applied to estimate MN_{50} $GMFR_{Post/Pre}$ and corresponding 95% CIs.
- MN50 GMTR between any two of study vaccine groups at Day 29 and the two-sided 95% CIs will be computed using analysis of covariance (ANCOVA), with the study vaccine group as the fixed effect and MN_{50} titer at Day 1 (adjusted for intergroup variation in baseline [pre-vaccination] MN_{50} titer) as the covariate under two-sided type I error rate of 0.05. No type I error rate adjustments will be made. The mean difference of all lots paired comparisons with their corresponding CI limits will then be exponentiated to obtain MN_{50} GMTR and the corresponding 95% CIs. Similar sample SAS code as IgG will be applied to estimate MN_{50} GMTR and corresponding 95% CIs.
- SCR is defined as proportion of participants who achieve seroconversion ≥ 4-fold increase from baseline in MN_{50} titers at Day 29. SCR in MN_{50} titers with corresponding two-sided exact binomial 95% CIs will be calculated using the Clopper-Pearson method with similar sample SAS code as IgG.
- Two-sided 95% CIs of the difference of SCRs in MN_{50} titers for all pairwise comparisons will be based on the Miettinen and Nurminen method with the similar sample SAS code as IgG.

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

As the 3rd secondary objectives, antibody responses in a hACE2 receptor-binding inhibition assay to the SARS-CoV-2 spike protein in previously vaccinated participants 18 to 49 years of age, the derived/calculated endpoints of hACE2 response will include hACE2 GMTs, $GMFR_{Post/Pre}$, and SCR will be summarized overall and by the study vaccine group, and between-group hACE2 GMTR and difference of SCRs in hACE2 titers for all pairwise comparisons will be calculated using the same statistical methods applied for MN50 titers.

7.2 Analyses of Secondary Endpoint of Safety

As the secondary objective, safety data include MAAEs and AESIs (including myocarditis and/or pericarditis) through Day 29 (ie, 28 days after vaccine dose) and SAEs throughout the study. All safety analyses will be descriptive and conducted using the Safety Analysis Set. Missing data will not be imputed.

MAAEs are defined as AEs with medically attended visits, including hospital, emergency room, urgent care clinic, or other visits to or from medical personnel for any reason. AESIs include PIMMCs, myocarditis or pericarditis (Listings in Appendix 3), AEs specific to COVID-19, or other potential AEs that may be determined at any time by regulatory authorities as additional information concerning COVID-19 is obtained (Listings in Appendix 2). SAE is defined as 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 Protocol.

Unsolicited MAAEs and AESIs through Day 29, and SAEs throughout the study will be summarized overall and by the study vaccine group and by SOC/PT using the latest version of MedDRA, as well as by severity (Mild, Moderate, Severe, or Potentially Life Threatening) 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 unsolicited AEs including MAAEs and AESIs through Day 29 will be summarized. A by-participant listing of MAAEs and AESIs through Day 29 and SAEs throughout the study will also be provided.

The following summaries of unsolicited AEs will be presented overall and by the study vaccine group as part of the primary analysis of safety:

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

7.3 Analysis of Exploratory Endpoints

The same statistical methods applied for the analysis of IgG, MN50, and hACE2 may also be applied to best characterize the immune response for future vaccine development needs to compare immune responses developed based on the assays used as the exploratory endpoints.

8 ADDITIONAL ANALYSES

8.1 Vital Signs

Vital sign measurements at all visits (Day 1 and Day 29) 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 and change from baseline in vital sign results will be presented overall and 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 will include height and weight, HEENT, neck, lungs, heart, cardiovascular, abdomen, and musculoskeletal system/extremities to allow for study vaccination. Symptom-directed (targeted) physical examination performed at all other scheduled time points (Day 1 and Day 29) 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

After all participants have completed throughout the study (from Day 1 through Day 29), and their data are cleaned, an analysis of all primary/secondary endpoints (IgG, MN_{50}, and hACE2) and all secondary safety endpoints through Day 29 will be conducted.

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/GMFR/GMTR/GMEU/GMEUR will be interpreted as analysis of the $\log_{10}$ of titer values or ELISA Units.

The individual IgG ELISA Units, immunogenicity (MN_{50}) titer values 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/GMFR/GMTR/GMEU/GMEUR 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 4 .

Table 4 Decimal Numbers for Parameters

Parameter	Number of Decimal
Number of participants (e.g., 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, $GMFR_{Post/Pre}$, their corresponding 95% CIs	1
GMEU, $GMFR_{Post/Pre}$, their corresponding 95% CIs	1
GMTR, GMEUR, their corresponding 95% CIs	2
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

GMTR/GMEUR between the study vaccine groups for all pairwise comparisons will be adjusted for pre-vaccination titer/ELISA unit.

11.3 Multiple Comparisons/Multiplicity

No multiplicity adjustment will be applied for the immunogenicity primary and secondary endpoints.

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 0 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.

12 CHANGES TO ANALYSES SPECIFIED IN THE PROTOCOL

13 REFERENCES

NVX-CoV2373 protocol
Version 5.0/Amendment 4 dated July 20, 2022

DAIDS 2017
Division of AIDS (DAIDS), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), US Department of Health and Human Services. Division of AIDS (DAIDS) table for grading the severity of adult and pediatric adverse events. July 2017. Available at: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf.

DaSilva 2013
DaSilva FT, DeKeyser FD, Lambert P-H, et al. Optimal approaches to data collection and analysis of potential immune mediated disorders in clinical trials of new vaccines. Vaccine. 2013;31:1870-1876.

Lambert 2020
Lambert P-H, Ambrosino DM, Andersen SR, et al. Consensus summary report for CEPI/BC March 12-13, 2020 meeting: Assessment of risk of disease enhancement with COVID-19 vaccines. Vaccine. 2020;38(31):4783-4791.

14 APPENDIX

Appendix 2 Schedule of Events for Study 2019nCoV-307

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

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

1. The Screening visit and Day 1 visit may be combined if feasible at any given study site.
2. EOS assessments will be conducted via on-site visit. Should participants decide to terminate early, a telephone call may occur to collect the maximum safety data possible.
3. Significant medical history should be recorded, including prior and ongoing medical conditions and significant surgical procedures.
4. Specific exclusions to study vaccination will be assessed before any vaccination. Waivers to enrolling participants with exclusions will not be given.

5. Recent (≤ 90 days) and current medications, including non-COVID-19 vaccines, should be recorded in the concomitant medication eCRF. All COVID-19 vaccines administered prior to screening should be recorded in the vaccine history eCRF.
6. Performed prior to study vaccination.
7. On vaccination day, participants will remain in the clinic or under study staff observation for at least 15 minutes post-vaccination to be monitored for any immediate hypersensitivity reactions.
8. Recording of SAEs, MAAEs, and AESIs (including potential immune-mediated medical conditions [PIMMCs] and myocarditis or pericarditis). See Table 4 for symptoms of myocarditis or pericarditis and Section 8.2.3.6 for instructions for follow-up.
9. EOS form will be completed for all participants, including participants who are terminated early.

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 in protocol). Note that this regulatory request is not specific to Novavax's qNIV or 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

Table 6 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 thyroiditis[a], diabetes mellitus type 1, Addison's disease.
Other Disorders:	Goodpasture syndrome, idiopathic pulmonary fibrosis, pernicious anemia, sarcoidosis.

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

AEs specific to COVID-19 are listed below (Table 7 in protocol). 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 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).

Appendix 3 Myocarditis and/or Pericarditis (CDC Definition)

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