STATISTICAL ANALYSIS PLAN

Protocol Title:	A Phase 3, Randomized, Double-Blinded Study to Evaluate the Safety and Immunogenicity of Omicron Subvariant and Bivalent SARS-CoV-2 rS Vaccines in Adolescents Previously Vaccinated with mRNA COVID-19 Vaccines
Protocol No.:	2019nCoV-314
Protocol Version No. / Date:	4.0 Amendment 2/ 21 August 2023
Sponsor:	Novavax, Inc 21 Firstfield Road Gaithersburg, MD 20878 United States [redacted]
SAP Version No. / Date:	V4.0 / 14 December 2023

CONFIDENTIALITY STATEMENT

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APPROVAL SIGNATURE PAGE

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Original Statistical Analysis Plan

Amended Statistical Analysis Plan [redacted]

SAP Originated By: [redacted]

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

[redacted]

[redacted] Date

[redacted]

[redacted] Date

[redacted]

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REVISIONS HISTORY

Version Number	Date	Revisions
1.0	28-July-2023	Initial version
2.0	26-September-2023	-List of abbreviation is updated. -Fixed typo in section 3.4 (number of subsets) and the title of section 3.4.4. -Added and updated mucosal objectives language to Table 2 and section 4.9.3. -Fixed typo in Table 2 where D28 was left out from the exploratory and secondary endpoints for serum hACE2 (Wuhan and XBB.1.5), IgG (Wuhan and XBB.1.5) and NAb (Wuhan). -Added section 4.2.4 Protocol Deviations Assessment for PP Analysis. - 'serum' is removed in section 3.4, as some assays are mucosal assays. -Updated in section 4.5.1 – solicited AEs beyond 7-day period will be collected using Continuing Solicited AE form. -Updated "first vaccination" to "study vaccination" in the SAP, as there is only one vaccination in the study.
3.0	19-October-2023	-Added post-hoc analysis requested by Health Canada -Updated interim analysis data extract and planned unblinding timeline from D28 to D56 visit in section 1.5.2.1 and section 7 so that the safety analysis will include 2-month safety follow-up data. -Updated that continuing solicited SAEs will be summarized separately in a listing. - Modified the name and the definition of the PP analysis subset for mucosal samples.
4.0	14-December-2023	-Change visit windows defined in section 4.2.4 for PP analysis exclusion to align with other studies.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
BMI	Body mass index
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CSR	Clinical Study Report
ELISA	Enzyme-linked immunosorbent assay
EOS	End of Study
FAS	Full Analysis Set
GCP	Good Clinical Practice
GMC	Geometric mean concentration
GMEU	Geometric mean ELISA unit
GMFR	Geometric mean fold rise
GMT	Geometric mean titer
GMTR	Geometric mean titer ratio (between groups)
hACE2	Human angiotensin-converting enzyme 2
ICH	International Council for Harmonisation
IgG	Immunoglobulin G
LB	Lower bound
IM	Intramuscular
IRT	Interactive Response Technology
LLOQ	Lower limit of quantification
MAAE	Medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
NAb	Neutralizing Antibody
mRNA	Messenger ribonucleic acid
NVX-CoV2373	Prototype vaccine with Matrix-M adjuvant
NVX-CoV2601	Omicron XBB.1.5 subvariant vaccine with Matrix-M adjuvant
PIMMC	Potential immune-mediated medical conditions
PCR	Polymerase chain reaction
PP	Per-Protocol
PT	Preferred term
r	Recombinant
RNA	Ribonucleic acid
S	Spike (protein)
SAE	Serious adverse event
SAP	Statistical analysis plan

Abbreviation	Definition
SARS-CoV	Severe acute respiratory syndrome coronavirus
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SARS-CoV-2 rS	Severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine
SAS	Statistical Analysis Software
SRR	Seroresponse rate
SOC	System organ class
TLF	Table, Listing, and Figure
ULOQ	Upper limit of quantification
WHO	World Health Organization

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide detailed descriptions of the statistical methods, data derivations, and data displays regarding the interim and final analysis for the study protocol 2019nCoV-314.The table of contents and templates for the TLFs will be produced in a separate document.

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

The preparation of this SAP has been based on International Conference on Harmonisation (ICH) E9 Statistical Principles for Clinical Trials and E6 Good Clinical Practice (GCP) guidelines.

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

1.1 Study Design

2019nCoV-314 is a Phase 3, randomized, observer blinded study to evaluate the safety and immunogenicity of a booster dose of Omicron XBB.1.5 subvariant SARS-CoV-2 rS vaccines adjuvanted with Matrix-M adjuvant in previously vaccinated participants.

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

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

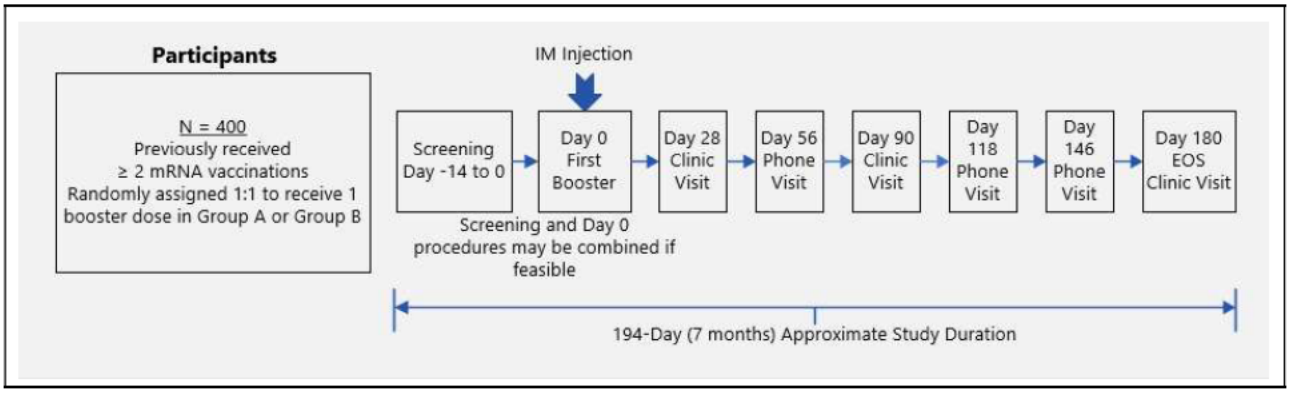
Participants will remain on study for immunogenicity and safety data collection through Day 180.

A tabular summary of the study design is provided below in Table 1 and study Schematic is shown in Figure 1.

Table 1: Study Groups and Treatments

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

Figure 1: Flow Diagram for Study 2019nCoV-314



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

1.2 Hypothesis

No formal hypothesis is required as the study objectives will be summarized descriptively.

1.3 Sample Size Considerations

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

1.4 Randomization and Treatment Assignments

An IRT will be responsible for the allocation of randomization numbers to individual participants. A copy of the randomization/enrollment code with true treatment allocations will be held by Syneos Health during the study. Another randomization/enrollment list (containing treatment) will be provided to clinical supplies. Randomization will be stratified by number of prior COVID-19 mRNA vaccinations received and study site.

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

Within each study site, participants will be randomized 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 (Sponsor and Syneos Health). As block size is considered potentially unblinding information, it will be known to the unblinded study Biostatistician only.

1.5 Blinding and Unblinding

1.5.1 Extent and Maintenance of Blinding

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

1.5.2 Unblinding Procedures

1.5.2.1 Planned Unblinding

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

An independent statistics organization or the internal sponsor statistics team will perform the analysis and receive unblinded data at the time of analyses, following final determination of subject exclusions from analysis populations and database extract. At the time of Day 56 data extract with receipt of the randomization list, the Sponsor will be unblinded at the participant level to prepare for regulatory submissions.

1.5.2.2 Participants Receiving Approved and/or Authorized COVID-19 Vaccines

Participants who wish to receive alternative booster vaccines approved and/or authorized for use by regulatory authorities governing study sites may be offered the opportunity to be unblinded so that they may receive the approved/authorized vaccine, as appropriate, outside the protocol procedures. Participants who wish to do so will be advised to discuss this plan with their healthcare provider. Participants who are unblinded and receive an approved/authorized vaccine in this manner will be strongly encouraged to remain in study for safety follow-up as defined in the protocol. However, participants also have the right to discontinue participation in the study at any time.

1.5.2.3 Unplanned or Unintentional Unblinding

A participant's vaccine assignment will not be revealed to the site study team until the time point described in the Planned unblinded section unless medical treatment of the participant depends on knowing the study vaccine the participant received. Should a situation arise where unblinding is required, the investigator at that study site has the sole authority to obtain immediate unblinding via the IRT. Prior to unblinding, or as soon thereafter as possible, the investigator should contact Syneos Health Medical Monitor to discuss the medical emergency and the reason for revealing the actual vaccine combination received by that participant. Emergency code breaks

performed using the IRT must be clearly explained and justified in the eCRF. The date on which the code was broken must also be documented.

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

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

Participants that are unblinded as a result of unplanned or unintentional unblinding will be excluded from the Per-Protocol Analysis Set.

2 STUDY OBJECTIVES AND ENDPOINTS

The primary objectives in this study are to assess the overall safety of 1 heterologous booster dose of NVX-CoV2601 and the bivalent vaccine (NVX-CoV2373 + NVX-CoV2601) and to describe the neutralizing antibody (NAb) responses induced against the Omicron XBB.1.5 subvariant. Participants will be medically stable male and nonpregnant females ≥ 12 to < 18 years of age who have previously received ≥ 2 doses of the Moderna and/or Pfizer-BioNTech monovalent and/or bivalent vaccines ≥ 90 days prior to study vaccination. Antibody titers resulting from a pseudovirus-based neutralization assay validated by the Novavax Clinical Immunology group will be used to evaluate the primary immunogenicity objective and endpoints. An overview of the study objectives and endpoints is provided in Table 2.

Table 2: Study 2019nCoV-314 Objectives and Endpoints

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

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Table 2: Study 2019nCoV-314 Objectives and Endpoints

Tier	Objectives	Endpoints
Primary Immunogenicity Objective and Endpoints	To describe the NAb response induced by NVX-CoV2601 and the bivalent vaccine (NVX-CoV2373 + NVX-CoV2601) against the Omicron XBB.1.5 strain.	NAb GMTs to the Omicron XBB.1.5 strain, assessed at Day 28 following initial study vaccination. NAb geometric mean fold rise (GMFR) at Day 28 from baseline (Day 0).
Secondary Objectives	To describe the NAb response induced by NVX-CoV2601 and the bivalent vaccine (NVX-CoV2373 + NVX-CoV2601) against the Omicron XBB.1.5 strain over time.	NAb GMTs to the Omicron XBB.1.5 strain at relevant time points (Days 0, 90, and 180). NAb GMFR at relevant time points (Days 90 and 180) from baseline (Day 0)
	To describe immunoglobulin G (IgG) antibody levels induced by NVX-CoV2601 and the bivalent vaccine (NVX-CoV2373 + NVX-CoV2601) against the Omicron XBB.1.5 strain over time.	IgG GMEUs to the Omicron XBB.1.5 S protein at relevant time points (Days 0, 28, 90, and 180). Derived/calculated endpoints based on these data will include GMFR.
Exploratory	To describe the NAb and IgG antibody responses induced by NVX-CoV2601 and the bivalent vaccine (NVX-CoV2373 + NVX-CoV2601) against the ancestral (Wuhan) strain over time.	NAb titers and IgG GMEUs to the ancestral (Wuhan) strain at relevant time points (Days 0, 28, 90, and 180). Derived/calculated endpoints based on these data will include GMFR.
	To describe antibody responses in a human angiotensin converting enzyme-2 (hACE2) receptor binding inhibition assay induced by NVX-CoV2601 and the bivalent vaccine (NVX-CoV2373 + NVX-CoV2601) to the Omicron XBB.1.5 and ancestral (Wuhan) strains over time.	GMTs to the Omicron XBB.1.5 and ancestral (Wuhan) strains at relevant time points (Days 0, 28, 90, and 180). Derived/calculated endpoints based on these data will include GMFR.
	To describe responses in a mucosal hACE2 receptor binding inhibition assay induced by NVX-CoV2601 and the bivalent vaccine (NVX-CoV2373 + NVX-CoV2601) to the Omicron XBB.1.5 and ancestral (Wuhan) strains over time.	GMTs to the Omicron XBB.1.5 and ancestral (Wuhan) strains at relevant time points (Days 0 and 28). Derived/calculated endpoints based on these data will include GMFR.

Table 2: Study 2019nCoV-314 Objectives and Endpoints

Tier	Objectives	Endpoints
Exploratory (cont.)	To describe antibody responses in a mucosal anti-spike IgA ELISA assay induced by NVX-CoV2601 and the bivalent vaccine (NVX-CoV2373 + NVX-CoV2601) to the Omicron XBB.1.5 and ancestral (Wuhan) strains over time.[1]	GMTs to the Omicron XBB.1.5 and ancestral (Wuhan) strains at relevant time points (Days 0 and 28). Derived/calculated endpoints based on these data will include GMFR.
	To utilize additional assays (current or to be developed) to better characterize the immune response for future vaccine development needs.	Additional endpoints to evaluate immune responses may be developed based on the assays used.
	To characterize the severity of COVID-19 in participants who become infected during the course of the study.	Detected case will be characterized as mild, moderate, or severe as assessed using the provided criteria.

Abbreviations: AE = adverse event; AESI = adverse event(s) of special interest; ELISA = enzyme-linked immunosorbent assay; GMEU = geometric mean ELISA units; GMFR = geometric mean fold rise; GMT = geometric mean titer; hACE2 = human angiotensin-converting enzyme 2; IgG = immunoglobulin G; NAb = neutralizing antibody; MAAE = medically attended adverse event; PIMMC = potentially immune-mediated medical condition; S = spike; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

[1] This objective is further clarified in the SAP that the saliva sample will be used for the mucosal anti-spike IgA ELISA assay in addition to the mucosal hACE2 receptor binding inhibition assay for the exploratory objective.

3 ANALYSIS SETS

3.1 All Randomized Participants Analysis Set

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

3.2 Full Analysis Set

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

3.3 Safety Analysis Set

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

3.4 Per-Protocol Analysis Set

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

Within the PP Analysis Set there are 4 subsets defined:

3.4.1 Anti-S Protein IgG Serology Subset (PP-S)

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

3.4.2 Neutralization Assay Subset (PP-N)

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

3.4.3 hACE2 Receptor-Binding Inhibition Assay Subset (PP-h)

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

3.4.4 Mucosal Sample Subset (PP-M)

All participants in the PP Analysis Set who have mucosal samples collected at each time point will be included in this subset.

4 STATISTICAL METHODS OF ANALYSIS

4.1 General Statistical Conventions

All statistical analyses will be completed using SAS version 9.4 or higher.

Unless otherwise stated, all statistical testing will be two-sided and will be performed using a significance level (alpha) of 0.05. P value (if presented) would be presented with 3 decimal places. If $P < 0.001$, it will be presented as '< 0.001'; if $P > 0.999$, it will be presented as '> 0.999'. Two-sided 95% confidence intervals (CI) will be provided when relevant.

Continuous variables will be summarized using descriptive statistics, including number of participants (n), mean, median, standard deviation (SD), minimum, and maximum. Means and medians will generally be rounded to one more decimal place than what is reported in the data.

Standard deviations will generally be rounded to two more decimal places than what is reported in the data.

Immunology data consisting of ELISA Unit (EU) and titer data will be summarized using geometric means, also known as geometric mean EUs/titers (GMEU/GMT), geometric mean fold rise (GMFR) and seroresponse rate (SRR). Immunology results below the lower limit of quantification (LLOQ) will be set as 0.5*LLOQ for the calculation of geometric means and GMFR. For seroresponse rate, the definition of a seroresponder is given in Section 4.9.1. Immunology results above the upper limit of quantification (ULOQ) will be summarized and reported using the ULOQ.

For categorical variables, summaries will include counts of participants and percentages. Percentages will generally be rounded to one decimal place. Confidence intervals surrounding proportions may be constructed using Clopper-Pearson method (for single groups), or the method of Miettinen-Nurminen (for between group difference), whichever is appropriate for the data.

For immunogenicity analysis, baseline will be the result from the sample drawn on the day of study vaccination. For all other analyses, baseline is defined as the last non-missing measurement prior to the administration of the study material. All summaries will be presented by the vaccine group, and stratification variable where appropriate, unless otherwise specified. Participant is considered PCR positive at baseline if any PCR results prior to vaccination is positive. Similarly, participant's baseline serostatus is considered positive if any anti-N-protein measurements prior to vaccination is positive.

All participant data, including those derived, will be presented in individual participant data listings. Unless otherwise stated, unscheduled visit results will be included in date/time chronological order, within participant listings only. All listings will be sorted by investigational site, participant ID, date/time and visit. The vaccine group will be presented when the study is unblinded at the subject-level; or if listings are provided to persons designated as able to view subject-level unblinded output. Unless otherwise stated, data listings will be based on all participants randomized.

Out of window data points will be reviewed during a review of protocol deviations, prior to unblinding, and a determination will be made as to whether that data point will be used in the analysis. Documentation and approval by the sponsor will be generated prior to unblinding.

4.2 Data Handling Conventions

4.2.1 Incorrect Randomization Stratum

Randomization is stratified by number of doses previously received (2 or 3) of the mRNA vaccines. Review of data collected on the CRF for previous mRNA vaccines received may indicate that participant has been randomized into the incorrect stratum. If this occurs, participants will be summarized based on actual number of doses of mRNA vaccines received.

The actual treatment received by participants may be different from the vaccine groups they are randomized to. Statistical summary will be based on randomized or actual vaccine groups depending on the analysis sets.

4.2.2 Rules to Handle Missing Data or Incomplete Dates.

Imputation rules for missing PCR, anti-N or immunogenicity results

Missing baseline PCR results will be imputed as negative ("not detected"). Missing baseline anti-N results will not be imputed. No imputations will be made for missing PCR results from nasal swabs collected at unscheduled visits. No missing data will be imputed for immunogenicity assay results.

Imputation rules for missing or partial AE start/stop dates

- If the AE start date day is missing (month and year provided) then set the date to the first of the month, unless the month and year are the same as a dosing event. In this case, set the date to the date of the dosing event.
- If the AE start date month is missing (year is provided) then set the month and day to January 1, unless the year is the same as the year of a dosing event. In this case, set the date to the earliest dosing event in that year.
- If the AE end date day is missing (month and year provided) then set the date to the last day of the month.
- If the AE end date month is missing (year is provided) then set the date to December 31.
- If the year of the AE start date or AE end date are missing, or imputed AE start date is not prior to AE end date, then a query to the site must be made to gather additional information. If the end date and start date are both missing, then no imputation will be done. If the start date remains missing but the end date is before first dose date, then the AE will be considered before treatment. If the end date is after the first dose, then the AE will be considered to have been treatment emergent.

Imputation rules for missing or partial medication or procedure start/stop dates

Start Date:

- If only day is missing, use the first day of the month.
- If day and month are missing, use the first day of the year.
- If day, month, and year are missing use the first day of the year with the same year as the first dose.

End Date:

- If only day is missing, use the last day of the month.
- If day and month are missing, use the last day of the year.
- If day, month, and year are missing assign 'continuing' status to the stop date.

Imputation rules for missing or partial medical history start dates

- 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 0 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.

4.2.3 Rules to Handle Duplicated Data

For immunogenicity data, if multiple non-missing values are available at the same visit, then the geometric mean of the eligible sample results will be used in the analysis.

For other qualitative lab data, if multiple records are available at the same visit with different collection date, use the one with non-missing value at later collection date/time in the analysis unless otherwise specified. In case where multiple records are on the same collection date/time but assay date/time is different, use the one with non-missing value at later assay date/time in the analysis unless otherwise specified. For other situation, the derivation will be determined per site or lab's instruction.

4.2.4 Protocol Deviations Assessment for PP Analysis

Protocol deviations deemed to indicate clear violations of GCP and/or subject consent; or to have a likely effect on the immunogenicity outcomes will exclude those participants from the corresponding PP analysis set. Prior to unblinding, the sponsor will review PDs to determine which participants will be excluded from the PP analysis.

In general, the following will be deemed "major" deviations relevant for analysis:

- Failure to obtain an executed and documented informed consent.
- Fraudulent or fabricated data.
- Inclusion criteria not met or exclusion criteria met that could result in an altered immune response.
- Failure to receive, or document receipt of, the study treatment as randomized.

- For inclusion in the PP analysis sets: serology sample missing or out-of-window that could introduce bias to the analysis or result in the inability to assay the sample.
- Administration of incorrect study vaccine.
- Administration of incorrect volume of vaccine or vaccine impacted by temperature excursion that could result in an altered immune response.
- Administration of expired vaccine per treatment arm.
- Anytime withdrawal criteria are met but participant was not withdrawn.
- Receipt of prohibited therapies within the specified timeframes of study conduct listed in Section 7.4.1 of the protocol that could result in an altered immune response:
  - No COVID-19 vaccines during the course of the study.
  - No other vaccines (except for a licensed seasonal influenza vaccine as described in the next bullet or rabies, HPV, Td, TDaP, Dtap, HBV, and meningococcal vaccines [if medically indicated]) will be allowed within 45 days prior to study vaccination or until 28 days after study vaccination.
  - No influenza vaccine will be allowed within 14 days prior to study vaccination and within 14 days after study vaccination.
  - No investigational product (drug/biologic/device) within 90 days prior to study vaccination until after the last study visit.
  - No chronic administration (defined as > 14 continuous days) of any immunosuppressant medication within 90 days prior to study vaccination until the last study visit (except topical or intranasal steroids, or short-term oral steroids with course lasting ≤ 14 days). Topical tacrolimus and ocular cyclosporine are permitted. Rabies immune globulin should be administered if medically indicated.

Serology collection visits that are missed or significantly out-of-window will be cross-checked against the visit dates collected in EDC, and in cases of discrepancies with protocol deviation descriptions, EDC data will take precedence.

Day 28 serology collection is significantly out of window and will be excluded from PP analysis if occurring more than 4 days prior to the target date for Day 28, or more than 14 days after the target date.

Day 90 serology collection is significantly out of window and will be excluded from PP analysis if occurring more than 14 days prior to the target date for Day 90, or more than 14 days after the target date.

Day 180 serology collection is significantly out of window and will be excluded from PP analysis if occurring more than 30 days prior to the target date for Day 180, or more than 30 days after the target date.

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4.3 Disposition and Protocol Compliance

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

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

The number (percentage) of participants who discontinue the study prior to EOS and the reason for discontinuation (e.g. AE, investigator decision, lost to follow-up, non-compliance, etc.), whether the vaccine is administered and the reason if not will be presented by vaccine group.

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

4.4 Demographics and Baseline Characteristics

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

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) terms (version 26.0). Baseline medical history recorded at Screening will be summarized by the study vaccine group and by MedDRA System Organ Class/Preferred Term (SOC/PT) for all participants in the Safety Analysis Set. Within each SOC and PT, the number and percentage of participants with at least one medical history event will be presented, respectively. Multiple events within a given SOC and PT for a participant will be counted once.

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

4.5 Safety Analyses

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

4.5.1 Solicited Adverse Events

The number and percentage (with two-sided exact 95% CIs using the Clopper-Pearson method) of participants with solicited injection site and systemic Aes through 7 days after vaccination will be summarized overall and by vaccine group and severity (i.e., by the worst maximum toxicity grade over 7 days after the vaccination [i.e., Days 0 – 6]). The durations of solicited local and systemic Aes after vaccination within the 7-day diary period and entire safety follow-up period will also be summarized by vaccine group. Summarization levels include any solicited AE, any solicited local AE, any solicited systemic AE, and individual reactions. For solicited AEs continuing beyond the 7-day diary period, then it will be recorded using the Continuing Solicited AE form (as described in Section 8.2.3.4 of the protocol).

4.5.2 Unsolicited Adverse Events

Unsolicited Aes will be coded by Primary System Organ Class (SOC) and Preferred Term (PT) using MedDRA (version 26.0).

Unsolicited Aes from the time of study vaccination through 28 days after vaccination will be summarized both overall and by vaccine group and by SOC/PT, as well as by severity and relationship to the study vaccine to present the number and percentage with corresponding exact 95% CIs using the Clopper-Pearson method. For multiple occurrences of an adverse event in the same participant, a participant will be counted only once, using the most severe or most related occurrence for the summarization by severity or relationship to the study vaccine, respectively. Adverse events will be sorted by descending rates within each SOC/PT according to the overall rate. Solicited Aes that extend beyond the initial 7-day diary period and are recorded using Continuing Solicited AE form (as described in Section 8.2.3.4 of the protocol) will not be included in summaries of unsolicited Aes. Continuing solicited Aes that become SAEs will be excluded from all unsolicited AE tables. A listing of excluded SAEs will be provided.

All MAAEs (all MAAEs for 28 days following vaccination and only related MAAEs beyond 28 days following vaccination), AESIs (predefined list in Appendix 1 of the study protocol) including Potential immune-mediated medical conditions (PIMMCs), AESIs relevant to COVID-19 and myocarditis/pericarditis, and SAEs throughout the study (up to the time of pre-planned analyses) will be summarized overall and by vaccine group as well as by severity. A summary of myocarditis and pericarditis events will be produced overall and by vaccine group.

Details for imputing missing or partial start dates of Aes are described in Section 4.2.2.

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4.5.3 Subgroup Analyses

Safety analyses may be performed by the following subgroups:

- Sex
- Race
- Ethnicity
- Number of prior COVID-19 mRNA vaccine received (2 doses vs. ≥ 3 doses)

4.6 Prior and Concomitant Medications

Prior and concomitant medications and vaccinations will be summarized overall and by vaccine group and preferred drug name as coded using the WHO drug dictionary (version March 2023 B3) for all participants on the Safety Analysis Set.

4.7 Extents of Exposure

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

4.8 Vital Sign Measurements and Physical Examination

Listings will be provided for vital sign measurements and physical examinations data collected in Safety Analysis Set.

4.9 Immunogenicity Analyses

All immunogenicity analyses will be descriptive. Listings will be provided for all immunogenicity data collected in Full Analysis Set.

4.9.1 Analysis of Primary Immunogenicity Endpoint

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

The primary immunogenicity endpoints focus on neutralizing antibodies (NAb) against the Omicron XBB1.5 strain at Day 28 following initial study vaccination. Neutralizing antibodies (NAb) GMT and GMFR (compared to Day 0) to the Omicron XBB.1.5 strain and corresponding 95% CIs, are summarized at Day 28 by vaccine group. GMT is calculated as the antilog of the mean of log-transformed titer values. GMFR is the antilog of the mean of log-transformed fold-rises. The 95% CIs are calculated based on the t-distribution of the log transformed titer or fold-

rise values, then back transformed to the original scale. The following is a sample of SAS code to compute the Geometric mean titer, GMFR and corresponding 95% CI.

```
Ods output Statistics=<output dataset>;
proc ttest data=<DATASET>;
   BY <trt visit>;  *change according to the table;
   var <log-transformed titer value>;
run;
ods output close;
```

The between-group ratio of GMT (GMTR) at Day 28 and the two-sided 95% CIs are computed using the analysis of covariance with the vaccine group as the fixed effect and the titer at Day 0 (ie, adjusted for intergroup variation in baseline [pre-vaccination] titers) as the covariate. The mean difference between vaccine groups and the corresponding CI limits will then be exponentiated to obtain the ratio of NAb GMTs and the corresponding 95% CIs. The following is a sample of SAS code to compute GMTR between vaccine groups:

```
proc mixed data= <DATASET>;
    class trt;
    model log(titer at Day 28) = log(titer at baseline) trt;
    lsmeans trt/cl diff e alpha=0.05;
run;
```

The percentage of participants achieving seroresponse (SRR) is calculated at Day 28. Seroresponse is defined as post-vaccination titer ≥ 4-fold increase from baseline value. Participants with a baseline value below the LLOQ will be considered achieving seroresponse only if the post-baseline value is greater than or equal to 4 times the LLOQ. Two-sided exact binomial 95% CIs will be calculated using the Clopper-Pearson method. The difference in SRR between groups will be calculated, with the 95% CI for the difference based on the method of Miettinen and Nurminen. There is no formal evaluation of statistical hypotheses. The following is a sample of SAS code to compute SRR and difference in SRR between vaccine groups and corresponding 95% CIs:

```
proc freq data=<DATASET>;
  by trt;
  tables seroresponse/ nocum norow binomial(level=2);
  exact binomial;
  ODS OUTPUT binomial=bin(where=(name1 in ('XL_BIN', 'XU_BIN')));
run;
proc freq data=<DATASET>;
  tables trt*seroresponse / riskdiff (CL=(MN));
  ods output PdiffCLs=risk_diff;
run;
```

4.9.2 Analysis of Secondary Immunogenicity Endpoints

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

summarized at Days 0, 90, and 180. NAb GMFR (compared to Day 0) and SRR to the Omicron XBB.1.5 strain and 95% CIs are summarized at Days 90 and 180.

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

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

Additional descriptive analyses of GMT, GMFR, and SRR may be performed by various subgroups:

- Baseline serostatus based on anti-N-Protein
- Number of prior COVID-19 mRNA vaccine received (2 doses vs $\geq$ 3 doses)

Graphical presentations of the data (e.g., reverse cumulative distribution curves, boxplots) may be generated.

4.9.3 Analysis of Exploratory Immunogenicity Endpoints

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

For the exploratory immunogenicity endpoints of antibody responses in a human angiotensin converting enzyme-2 (hACE2) receptor binding inhibition assay against the Omicron XBB.1.5 and ancestral (Wuhan) strains over time, analyses will be performed using the Per-Protocol (PP) Analysis Set and the hACE2 Receptor-Binding Inhibition Assay Subset. hACE2 GMTs to the Omicron XBB.1.5 and ancestral (Wuhan) strains with corresponding 95% CIs are summarized at Days 0, 28, 90, and 180. hACE2 GMFR (compared to Day 0) and SRR to the Omicron XBB.1.5 and ancestral (Wuhan) strains with corresponding 95% CIs are summarized at Days 28, 90, and 180. The endpoints will be analyzed by vaccine group.

Mucosal hACE2 receptor binding inhibition and mucosal anti-spike IgA ELISA responses to the Omicron XBB.1.5 and ancestral (Wuhan) strains will be summarized using the PP Analysis Set and the Mucosal Sample Subset. GMTs to the Omicron XBB.1.5 and ancestral (Wuhan) strains

with corresponding 95% CIs will be summarized at Days 0 and Day 28. GMFR (compared to Day 0) and SRR with corresponding 95% CIs will be summarized at Day 28.

Additional immunogenicity assay results against existing or future variants may be analyzed analogously.

Graphical presentations of the analyses (e.g., boxplots, reverse cumulative distribution curves) may be generated.

5 OTHER EXPLORATORY ANALYSES

Number of participants who reported COVID-19 event and number of reported events will be summarized. Events will be summarized by these factors - including but not limited to severity and type of diagnostic. Time of event since vaccination is defined as the interval between dosing and non-missing illness start date or positive test date associated with the event, whichever happens earlier. Mean, median, minimum and maximum will be provided. Demographics for participants with event(s) including but not limited to sex, race and ethnicity will be summarized.

For this objective, a COVID-19 event is defined as mild, moderate or severe COVID-19 disease confirmed by diagnostic test with onset from the date of vaccination to the date of earliest of (i) cut-off date, (ii) study termination. The number will be presented by vaccine group on the Safety Analysis Set.

6 POST-HOC ANALYSIS

The following post-hoc analysis were requested by Health Canada, dated 26 September 2023.

- Analysis of the neutralizing antibodies at 28 days post-dose of the "per-protocol immunogenicity" population that received NUVAXOVID XBB.1.5 compared to the historical control of adolescents that received NUVAXOVID (prototype vaccine) as a third booster dose following the NUVAXOVID primary series.
- Analysis of the safety, namely, 7-day reactogenicity (local and systemic adverse event) and 28-day treatment emergent adverse events, in the safety analysis set population that received NUVAXOVID XBB.1.5 compared to the historical control of adolescents that received NUVAXOVID (prototype vaccine) as a third booster dose following the NUVAXOVID primary series.

A subset of approximately 110 participants from the 301 PEDS study are selected and tested for NAb response against Omicron XBB.1.5 and/or Wuhan strain. NAb GMTs and 95% CIs are summarized at Day 0 and Day 28. NAb GMFR (compared to Day 0) and SRR and 95% CIs are summarized. GMTR and difference in SRR (compared to participants who received NVX-CoV2601 in the PP analysis set and within the Neutralization Assay Subset) at Day 28 and the two-sided 95% CIs are calculated.

7-day reactogenicity and 28-day treatment emergent adverse events for participants in the 301 PEDS study safety analysis set are summarized and compared to participants that received NUVAXOVID XBB.1.5 in the 314 study.

The post-hoc analysis will be descriptive in nature.

7 STATISTICAL CONSIDERATIONS FOR INTERIM ANALYSES

A formal interim analysis will be carried out when the complete data is available to evaluate the primary endpoint and 2-month safety follow-up. A set of secondary and exploratory endpoints will also be analyzed at this time, dependent on the availability of data. The database extract is expected to include immunogenicity data through Day 28 and safety data through Day 56. An independent statistics organization or the internal statistics team will perform the analysis and receive unblinded data at the time of analyses, following final determination of participant exclusions from analysis populations and database extract. At the time of Day 56 data extract with receipt of the randomization list, the Sponsor will be unblinded at the participant level to prepare for regulatory submissions.

8 CHANGES TO ANALYSES SPECIFIED IN THE PROTOCOL

- A typo was found in the Protocol v4.0, Table 2: Study 2019nCoV-314 Objectives and Endpoints – Day 28 timepoint was inadvertently left out for serum hACE2 (Wuhan and XBB.1.5), IgG (Wuhan and XBB.1.5) and NAb (Wuhan) in the exploratory and secondary endpoints. This has been updated in the SAP v2.0, Table 2.
- Interim Analysis data extract and planned unblinding timeline is updated from Day 28 to Day 56 visit to include 2-month safety data.
- Modified the name and the definition of the PP analysis subset for mucosal samples.

9 REFERENCES

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10 APPENDIX

10.1 Appendix 1: Toxicity Grading Scale for Clinical Abnormalities (local and general systemic reactogenicity, clinical laboratory, and vital signs)

Table 3: Modified FDA Toxicity Grading Scale for Clinical Abnormalities (Local and General Systemic Reactogenicity)

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

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

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

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

Source: FDA 2007

Table 4: FDA Toxicity Grading Scale for Clinical Abnormalities (Vital Signs)

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

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

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

Source: FDA 2007