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A PHASE 1/2, RANDOMIZED, OBSERVER-BLINDED STUDY TO EVALUATE THE SAFETY AND IMMUNOGENICITY OF A QUADRIVALENT HEMAGGLUTININ NANOPARTICLE INFLUENZA AND SARS-COV-2 RS NANOPARTICLE COMBINATION VACCINE WITH MATRIX-M1™ ADJUVANT IN HEALTHY PARTICIPANTS ≥ 50 TO ≤ 70 YEARS OF AGE

Novavax Protocol Number: **2019nCoV-ICC-E-101**

STATISTICAL ANALYSIS PLAN (SAP) for Day 70 and Final Analysis of Safety and Immunogenicity Data

SAP Version and Date: Version 2.0 – 28 January 2022

Investigational Product:

- Quadrivalent Hemagglutinin Nanoparticle Influenza Vaccine (qNIV) (containing the World Health Organization recommended strains for the 2019 - 2020 northern hemisphere influenza season, ie, A/Brisbane/02/2018 [H1N1] pdm09; A/Kansas/14/2017 [H3N2]; B/Maryland/15/2016; B/Phuket/3073/2013) with Matrix-M1™ adjuvant
- SARS-CoV-2 rS Nanoparticle Vaccine with Matrix-M1 Adjuvant
- qNIV and SARS-CoV-2 rS Nanoparticle Vaccine with Matrix-M1 Adjuvant

APPROVAL SIGNATURE PAGE

Protocol Number:	2019nCoV-ICC-E-101
Protocol Version and Date:	Version 2.0 - <19 July 2021>
Protocol Title:	A Phase 1/2, Randomized, Observer-Blinded Study to Evaluate the Safety and Immunogenicity of a Quadrivalent Hemagglutinin Nanoparticle Influenza and SARS-CoV-2 rS Nanoparticle Combination Vaccine with Matrix-M1™ Adjuvant in Healthy Participants ≥ 50 to ≤ 70 years of Age
SAP Version and Date:	Version 2.0 – 28 January 2022

☐ Original Statistical Analysis Plan

☒ Amended Statistical Analysis Plan

SAP Originated By: [redacted]

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

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Clinical Development Medical Lead

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Signed Electronically

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Project Statistician

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LIST OF ABBREVIATIONS

Abbreviation or Term	Definition
AE	Adverse event
AESI	Adverse event of special interest
BMI	Body mass index
CI	Confidence interval
CMI	Cell-mediated immunity
COVID-19	Coronavirus disease 2019
CSR	Clinical Study Report
DAIDS	Division of AIDS, NIAID, NIH
DoE	Design of Experiments
eCRF	Electronic case report form
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
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
HAI	Hemagglutination inhibition
HIV	Human immunodeficiency virus
ICC	Influenza COVID-19 combination
ICCS	Intracellular cytokine staining
ICF	Informed consent form
ICH	International Council for Harmonisation
IgG	Immunoglobulin G
IM	Intramuscular

Abbreviation or Term	Definition
IWRS	Interactive Web Response System
LLOQ	Lower limit of quantification
MAAE	Medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MN	Microneutralization (assay)
MN_{50}	Microneutralization assay with an inhibitory concentration of 50%
NP	Nucleoprotein
NI	Non-inferiority
NIAID	National Institutes of Allergy and Infectious Diseases
NIH	National Institutes of Health
NIV	Nanoparticle influenza vaccine
NVX-CoV2373	SARS-CoV-2 rS with Matrix-M1 adjuvant
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
PIMMC	Potential immune-mediated medical conditions
PP	Per-Protocol
PT	Preferred term
qNIV	Quadrivalent hemagglutinin nanoparticle influenza vaccine
r	Recombinant
rS	recombinant spike (protein)
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
SPR	Seroprotection rate
TEAE	Treatment-emergent adverse event
Th1	Type 1 T helper
Th2	Type 2 T helper
VLP	Virus-like particle

Abbreviation or Term	Definition
WHO	World Health Organization

1 INTRODUCTION

Novavax is developing a novel recombinant qNIV with Matrix-M1 adjuvant for the prevention of disease due to influenza virus in adults ≥ 65 years of age, using a recombinant baculovirus and insect cell vaccine platform technology. In a recent Phase 3 study (qNIV-E-301; NCT**04120194**), qNIV with Matrix-M1 adjuvant demonstrated an acceptable safety profile, immunologic non-inferiority (NI) to quadrivalent inactivated influenza vaccine (IIV4) based on egg-based hemagglutination inhibition (HAI) antibody responses against 4 vaccine-homologous strains, and 34% to 46% higher wild-type HAI antibody responses against 6 heterologous A(H3N2) strains. Additionally, qNIV with Matrix-M1 adjuvant showed a 126% to 189% improvement in various post-vaccination antigen-specific CD4+ T-cell markers compared to that for IIV4.

In response to the coronavirus disease 2019 (COVID-19) pandemic caused by the emergence of SARS-CoV-2, Novavax is also developing SARS-CoV-2 rS with Matrix-M1 adjuvant for the prevention of COVID-19 in adults ≥ 18 years of age, using the same recombinant baculovirus and insect cell vaccine platform technology employed to produce qNIV. Both nonclinical and clinical data to date support continued clinical development of SARS-CoV-2 rS with Matrix-M1 adjuvant. In an ongoing Phase 1/2 study involving healthy adults in the United States (US) and Australia (2019nCoV-101; NCT04368988), 5 µg and 25 µg SARS-CoV-2 rS with 50 µg Matrix-M1 adjuvant demonstrated an acceptable safety profile and was associated with strong neutralizing-antibody and Type 1 T helper (Th1)-based antigen-specific polyfunctional CD4+ T-cell responses in participants 18 to 84 years of age. In an ongoing 15,000-person Phase 3 efficacy study in healthy and medically stable adult participants 18 to 84 years of age in the United Kingdom (UK) (2019nCoV-302; NCT04583995), the overall efficacy of 5 µg SARS-CoV-2 rS with 50 µg Matrix-M1 adjuvant was 89.7% (95% confidence interval [CI]: 80.2, 94.6) and, in post hoc analyses, efficacy estimates for the B.1.1.7 (Alpha) variant and for the original strain were 86.3% and 96.4%, respectively. In an ongoing 4,400-person Phase 2b efficacy study in healthy human immunodeficiency virus (HIV)-negative adult participants 18 to 84 years of age and medically stable HIV-positive adult participants 18 to 64 years of age in South Africa (2019nCoV-501; NCT04533399) conducted during a period of > 94% B.1.351 (Beta) variant virus circulation, the efficacy of 5 µg SARS-CoV-2 rS with 50 µg Matrix-M1 adjuvant in all study participants was 48.6% (95% CI: 28.4, 63.1) and 55.4% (95% CI: 35.9, 68.9) in participants who were HIV-negative. In an ongoing 30,000-person Phase 3 efficacy study in healthy and medically stable adult participants ≥ 18 years of age in the US, Mexico, and Puerto Rico (2019nCoV-301; NCT04611802), the overall efficacy of 5 µg SARS-CoV-2 rS with 50 µg Matrix-M1 adjuvant was 90.4% (95% CI: 82.9, 94.6) against symptomatic COVID-19 and 100% (95% CI: 87.0, 100) against moderate or severe COVID-19. Across all clinical studies conducted to date, SARS-CoV-2 rS with Matrix-M1 adjuvant has continued to demonstrate good tolerability and an acceptable safety profile.

In anticipation of a future need to immunize against both SARS-CoV-2 and influenza virus in advance of the winter transmission season, Novavax is undertaking development of an ICC (ie, qNIV and SARS-CoV-2 rS with Matrix^{-}M1 adjuvant). An ICC vaccine would address 2 major vaccine-preventable diseases with a single vaccination approach. The initial target

population for ICC vaccine development is older adults because this population bears a disproportionate burden of morbidity and mortality due to both influenza and COVID-19.

The purpose of this Phase 1/2 study is to evaluate the safety and immunogenicity of multiple formulations of ICC vaccines in older adults. The main objective of the study is to identify one or more optimal dose levels of HA and rS antigens administered as a combination vaccine, which minimize both antigen doses and manage any immunologic interference, using a DoE modeling approach.

1.1 Study Design

This is a randomized, observer-blinded, Phase 1/2 study evaluating the safety and immunogenicity of a quadrivalent hemagglutinin (HA) nanoparticle influenza vaccine (qNIV) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) recombinant spike (rS) nanoparticle combination vaccine with Matrix-M1™ adjuvant; this combination vaccine is referred to as Influenza COVID-19 Combination (ICC) vaccine.

The study will enroll approximately 640 healthy (based on history and physical examination) adult male and female participants 50 to 70 years of age, inclusive, targeting participants who are baseline seropositive (either previously infected with SARS-CoV-2 ≥ 8 weeks prior to enrollment, or have been previously immunized against SARS-CoV-2 with a completed regimen of an authorized vaccine at ≥ 8 weeks prior to enrollment). Randomization will be stratified on age ≥ 50 to <60 or ≥ 60 to ≤ 70 years to distribute the proportions of each age stratum evenly across vaccine groups.

Participants will be simultaneously enrolled and randomly assigned equally into 1 of 16 vaccine groups as per the Study Design Table (Table). The doses of the influenza and SARS-CoV-2 rS components included in the various vaccine groups have been selected based on the known performance of the antigens separately and the ability to obtain response data over a broad range of mixtures. These data will in turn be used in statistical modeling to predict one, or a few, optimal formulations for further clinical testing.

Table 1 Number of Participants and Dosing Regimens

Vaccine Group[1]	N[2]	Day 0			Day 56 (± 4 days)		
		HA Dose per Strain, µg	rS, µg	Matrix-M1, µg	HA Dose per Strain, µg	rS, µg	Matrix-M1, µg
ICC vaccine formulations							
A	40	60	22.5	50	60	22.5	50
B	40	10	2.5	50	10	2.5	50
C	40	60	22.5	50	60	22.5	50
D	40	10	7.5	50	10	7.5	50
E	40	10	22.5	50	10	22.5	50
F	40	35	7.5	50	35	7.5	50
G	40	5	22.5	50	5	22.5	50
H	40	60	2.5	50	60	2.5	50

Table 1 Number of Participants and Dosing Regimens

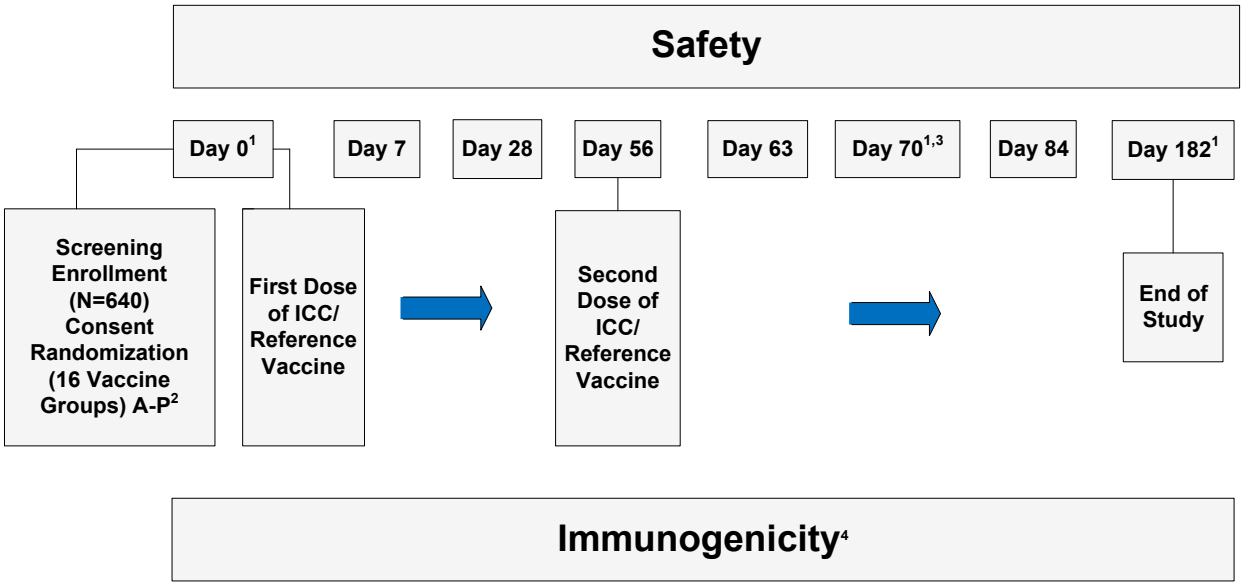
Vaccine Group[1]	N[2]	Day 0			Day 56 (± 4 days)		
		HA Dose per Strain, µg	rS, µg	Matrix-M1, µg	HA Dose per Strain, µg	rS, µg	Matrix-M1, µg
I	40	5	7.5	50	5	7.5	50
J	40	5	2.5	50	5	2.5	50
K	40	35	22.5	50	35	22.5	50
L	40	35	2.5	50	35	2.5	50
M	40	60	7.5	50	60	7.5	50
N	40	60	2.5	50	60	2.5	50
qNIV with Matrix-M1 adjuvant reference formulation							
O[3]	40	60	0	75	0	5	50
SARS-CoV-2 rS with Matrix-M1 adjuvant reference							
P	40	0	5	50	0	5	50
Total	640						

Abbreviations: COVID-19 = coronavirus disease 2019; HA = hemagglutinin; rS = recombinant spike protein; qNIV = quadrivalent hemagglutinin nanoparticle influenza vaccine; SARS-CoV-2 rS = severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine.

1. Antigen and adjuvant dose values are nominal and reflect target doses. Details of the final product in-clinic mixing scheme, the actual content of doses achieved by the in-clinic mixing of drug product lots, and injected volumes used are provided in the Study Pharmacy Manual.
2. Due to uncertainties in the pace of national SARS-CoV-2 vaccine deployment and evolving COVID-19 epidemic conditions, it is acknowledged that the targeted sample size for the study may be revised in response to the impact these evolving conditions may have on enrollment.
3. Participants from Vaccine Group O will receive an additional dose of 5 µg SARS-CoV-2 rS with 50 µg Matrix-M1 at Day 70.

All participants in Vaccine groups A through P (Figure 1, Appendix 1) will receive 2 intramuscular (IM) doses of the investigational combination vaccine, the first on Day 0 and the second on Day 56 (± 4 days) and remain on study for immunogenicity and safety data collection through Day 182 (End of Study [EoS]); participants in Vaccine Group O will receive an additional IM dose of 5 µg SARS-CoV-2 rS with 50 µg Matrix-M1 adjuvant on Day 70 to ensure this group receives 2 doses of COVID-19 vaccine. The key informative immunogenicity time points for antibody responses will be Days 0 and 70 (14 days post-second dose), and for cell-mediated immunity (CMI) will be Days 0 and 63 (7 days post-second dose). Reference formulations of 60 µg HA/strain qNIV with 75 µg Matrix-M1 adjuvant and 5µg SARS-CoV-2 rS with 50 µg Matrix-M1 adjuvant will be included as vaccine groups to benchmark optimal immune responses to each antigen administered as a standalone vaccine.

Figure 1 Flow Diagram for Study 2019nCoV-ICC-E-101



Abbreviations: COVID-19 = coronavirus disease 2019; HAI = hemagglutination inhibition; ICC = influenza COVID-19 combination; NP = nucleoprotein; PBMC = peripheral blood mononuclear cell; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SARS-CoV-2 rS = severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine; SOE = Schedule of Events.

1. SARS-CoV-2 anti-NP antibodies to be assessed.
2. Consisting of 14 formulations of ICC vaccine (comprising 12 unique formulations and 2 pairs of duplicated formulations) and 2 reference vaccines.
3. Participants from Vaccine Group O only will receive a third dose of COVID-19 vaccine consisting of 5 µg SARS-CoV-2 rS nanoparticle vaccine and 50 µg Matrix-M1 adjuvant at Day 70.
4. PBMCs will be harvested for SARS-CoV-2 spike-specific T-cell counts on Days 0, 7, 63, and 182. See the SOE for the timing of HAI serology and the remaining immunogenicity assessments.

The study will enable selection of one or more optimized ICC vaccine formulations (through Design of Experiments [DoE] response surface modeling) to advance into further development for dose/formulation confirmation in a future Phase 2 study.

1.2 Sample Size Considerations

The sample size of 40 participants per group for this study is based on clinical and practical considerations and not on a formal statistical power calculation. This distribution of participants would provide a sufficient number of replicates per set of factor levels studied in the DoE approach to account for expected variability in the immune responses due to elements such as subject and assay variability. There were no formal power calculations based on the DoE analysis methods. As an informal way to measure the approximate number of replicates (ie, participants) needed per vaccine formulation, the data from HAI testing with VLP reagents from the qNIV-E-301 study for 4 vaccine-homologous and 7 vaccine-nonhomologous strains will be used to average the fold rise at Day 28 to provide input to a sample size calculation to detect a two-fold difference in response relative to baseline. This calculation showed that a sample size of 40 would provide > 99% power to differentiate the immune response between two formulations.

With 40 participants in each treatment group, there is 87% probability to observe at least 1 participant with an AE if the true incidence of the AE is 5%. With 560 participants receiving

a combination formulation of influenza and SARS-CoV-2 vaccine, an AE with true incidence of 0.534% can be detected with 95% probability.

1.3 Randomization and Treatment Assignments

An Interactive Web Response System (IWRS) will be responsible for the allocation of randomization numbers to individual participants. Randomization will be stratified on age ≥ 50 to <60 or ≥ 60 to ≤ 70 years to distribute the proportions of each age stratum evenly across vaccine groups. Prior to production, the randomization specification will be reviewed and agreed by the study team (Sponsor and PPD). As block size is considered potentially unblinding information, it will be known to the Novavax Study Biostatistician only.

Randomization will take place at Day 0 after confirmation that the participant meets the inclusion/exclusion criteria. Participants will be randomly assigned to receive monovalent SARS-CoV-2 rS with Matrix-M1 adjuvant, qNIV with Matrix-M1 adjuvant, or qNIV + SARS-CoV-2 rS with Matrix-M1 adjuvant (Table).

1.4 Blinding and Unblinding

This is an observer-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.

A participant's vaccine assignment will not be revealed to the site study team until the end of the study (defined as the date on which the last participant completes the last study visit including the EoS visit and any additional long-term follow-up) 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 IWRS. Emergency code breaks performed using the IWRS must be clearly explained and justified in the eCRF. The date on which the code was broken must also be documented. The system will automatically inform the Protocol safety Review Team, PPD Site Monitor, the PPD Medical Monitor, and the PPD Project Manager that the code has been broken, but no treatment assignment will be communicated.

Participants are asked not to receive approved/authorized COVID-19 vaccines for the duration of study follow-up, and in particular, through Day 84, so as not to cofound assessment of immune responses to ICC vaccine. However, for participants who received the Novavax investigational vaccine and who nonetheless wish to receive an approved/authorized COVID-19 vaccine from another manufacturer will be advised to discuss this plan with their healthcare provider given the current lack of safety data regarding the sequential administration of vaccines made by different manufacturers. Participants who want to receive an approved/authorized vaccine in this manner will be strongly encouraged do so only after Day 84 and will 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.

At the time of the Day 70 analysis, upon final determination of subject exclusions from analysis and data extraction, members of the Novavax Biostatistics team will be unblinded to perform the analysis. Unblinded data include randomization assignment, dosing received at each dosing visit, and immunological testing results. The broader Novavax team will be group-unblinded upon the release of analysis results.

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-ICC-E-10 Version 2.0, dated 19 July 2021, and will address the analysis presentation of the Day 70 analysis review as well as the final EoS analysis review of all data through Day 182 for the completed study.

Day 70 analysis review will be conducted upon completion of all Day 70 visits for all vaccine groups, which will include all primary endpoints data of safety through Day 70, secondary/exploratory endpoints of immunogenicity (HAI, MN_{50}, IgG) through Day 70 and may include CMI through Day 63. Immunogenicity Data will also be used in the response surface modeling covered under the exploratory analysis.

Final EoS analysis review will be conducted when all available safety and immunogenicity data through Day 182 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 **Error! Reference source not found.**.

Table 1 Study 2019nCoV-E-101: Primary, Secondary, and Exploratory Objectives and Endpoints

Tier	Objectives	Endpoints
Primary Safety	To describe the tolerability and safety profiles associated with the receipt of the multiple vaccine formulations/regimens included in the study. Safety profiles will include: • Solicited AEs over 7 days after each of the first and second doses (including immediate AEs in the 30 minutes after dosing), to encompass both local injection site symptoms/signs and systemic symptoms/signs. • Unsolicited AEs over 70 days after the first dose. • MAAEs, SAEs, and AESIs over 6 months (approximately 182 days) after first dose.	• Numbers and percentages (with 95% CIs) of participants with solicited local and systemic AEs over the 7 days post-injection after first and second doses. • Proportions of participants reporting all AEs, solicited and unsolicited over 70 days after first dose. • Proportions of participants with MAAEs, SAEs, and AESIs will be collected for 6 months after the first dose.

Table 1 Study 2019nCoV-E-101: Primary, Secondary, and Exploratory Objectives and Endpoints

Tier	Objectives	Endpoints
Secondary Immunogenicity	To describe the immune response to immunization with various vaccine formulations/regimens at approximately Day 28 (post-first dose), Day 56, and Day 70 (post-second dose), and other follow-up time points, in terms of the: • Influenza HAI antibody responses (assayed with wild-type VLP reagents) against 4 vaccine-homologous strains, and at least 1 antigenically drifted A or B strain • Influenza MN antibody responses (assayed with wild-type virus) against 4 vaccine-homologous strains, and at least 1 antigenically drifted A or B strain • SARS-CoV-2 anti-S IgG antibody responses to vaccine homologous virus antigen. Cross-reactive responses to virus variants may be assessed if available. • SARS-CoV-2 neutralizing antibody responses to vaccine homologous virus. Cross-reactive responses to virus variants may be assessed if available.	HAI antibody titers specific for the HA receptor binding domains of vaccine-homologous A and B strain(s), and antigenically drifted influenza strains. Derived/calculated endpoints based on these data will include: • GMT, defined as the antilog of the mean of the log-transformed HAI titers on Days 56, 70, and other follow-up time points. • $GMFR_{Post/Pre}$ – defined as the within group ratio of post-vaccination to pre-vaccination (Day 0) HAI GMTs, within the same vaccine group on Days 56, 70, and other follow-up time points. • SCR – defined as proportion of participants in a given treatment group with either a baseline reciprocal (Day 0) titer of < 10 and a post-vaccination reciprocal titer ≥ 40, or a baseline reciprocal (Day 0) titer of ≥ 10 and a post-vaccination titer $\geq$ 4-fold higher than the baseline titer as measured on Days 56, 70, and other follow-up time points. • SPR – defined as the proportion of participants with a reciprocal HAI titer ≥ 40 on Days 56, 70, and other follow-up time points. • GMTR between select treatment arms at Days 56, 70, and other follow-up time points post-vaccination (adjusted for intergroup variation in baseline [pre-vaccination] titers). MN_{50} antibody responses: neutralizing antibody titers specific to vaccine homologous wild-type A and B strain(s) and/or antigenically drifted influenza strains, as measured by a MN assay. Derived/ calculated endpoints for GMT, GMFR, SCR, and GMTR will be defined in manner similar to HAI antibodies described above. IgG geometric mean ELISA unit concentrations (EU/mL) to the SARS-CoV-2 S protein from the matched vaccine construct

Table 1 Study 2019nCoV-E-101: Primary, Secondary, and Exploratory Objectives and Endpoints

Tier	Objectives	Endpoints
		(and mismatched variant if available), at Days 0, 56, 70, and other follow-up time points. Derived/calculated endpoints for GMEU, GMFR, and SCR and GMEUR will be defined in manner similar to that for HAI antibodies described above. MN_{50} GMTs to the SARS-CoV-2 from the matched vaccine construct (and mismatched variant if available), at Days 0, 56, 70, and other follow-up time points. Derived/ calculated endpoints for GMT, GMFR, SCR, and GMTR will be defined in manner similar to that for HAI antibodies described above.
	To determine one or more optimal dose levels of HA and rS antigens delivered in combination that maximize HAI antibody and anti-S antibody responses using a DoE modeling approach.	Post-vaccination time point HAI and anti-S antibody responses (eg, ratio of post-vaccination to pre-vaccination antibody levels) used to construct separate models of HAI and anti-S responses, respectively, to assess primary effects of each antigen's dose level and interactive effects between dose levels of the 2 antigens. Modeled responses in turn used to optimize dose levels of each antigen in relation to the other to maximize HAI and anti-S antibody responses.
Exploratory Immunogenicity	To describe the CMI responses to the various formulations/regimens in terms of peripheral blood CD4+ T cells which elaborate one or more cytokines or activation markers (IL-2, TNFα, IFNγ, or CD40L) in response to in-vitro stimulation with either strain-specific HAs and/or rS. Other markers of CMI may be measured. Due to the laborious nature of the CMI assays, they will be performed on all participants drawn from a limited number of preselected sites and results may be reported as an addendum to the main clinical study report. (Note: multiple informative strains may be tested in informative random subsets of participants)	Counts and/or proportions of Days 0, 7, 63, and 182 peripheral blood effector memory T-cell populations that secrete/express one or more of IL-2, CD40L, IFNγ, and TNFα cytokines following in-vitro restimulation with strain specific HAs and/or rS in participants selected for CMI response monitoring. Counts and/or proportions of additional markers of CMI as appropriate.
	To utilize additional assays (current or to be developed) to best characterize the immune response for future vaccine development needs	Additional endpoints to evaluate immune responses may be developed based on the assays used.

Table 1 Study 2019nCoV-E-101: Primary, Secondary, and Exploratory Objectives and Endpoints

Tier	Objectives	Endpoints
Abbreviations: AE = adverse event; AESI = adverse event of special interest; CD40L = CD40 ligand; CI = confidence interval; CMI = cell-mediated immunity; DoE = Design of Experiments; ELISA = enzyme-linked immunosorbent assay; EU = ELISA unit; GMEU = geometric mean ELISA unit; GMEUR = geometric mean ELISA unit ratio; GMFR = geometric mean fold rise; GMT = geometric mean titer; GMTR = geometric mean titer ratio; HA = hemagglutinin; HAI = hemagglutination inhibition; IgG = immunoglobulin G; IL = interleukin; IFNγ = interferon gamma; MAAE = medically attended adverse event; MN = microneutralization; rS = recombinant spike protein; S = spike; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SCR = seroconversion rate; SPR = seroprotection rate; TNFα = tumor necrosis factor alpha; VLP = virus-like particle.		

3 ANALYSIS SUBSETS

3.1 All Randomized Participants Analysis Set

The Randomized Participants Analysis Set (hereafter referenced as "Randomized Set") will include all participants who provide consent and are randomly assigned to treatment, regardless of whether they actually received any study vaccine. The Randomized Set will be used for participant disposition summaries and will be analyzed according to the treatment as randomized.

3.2 Full Analysis Set

The Full Analysis Set (FAS) will include all participants from the Randomized Set who received at least 1 dose of study vaccine, regardless of protocol violations or missing data. The FAS would be the analysis set used for supportive 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 from the Randomized Set 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 for immunogenicity is a subset of participants from the FAS and will be determined for each study visit. The PP Analysis Set will include all participants who receive the full prescribed regimen of the study vaccine according to the protocol, have blood collected for immunogenicity assessment for baseline and at least 1 post-vaccination time point, and have no major protocol violations that are considered clinically relevant to impact immunogenicity response as determined prior to database freeze for analysis. For time points after Day 56, participants must have received both doses of study vaccine to be included in the PP Analysis Set.

Within the PP Analysis Set there are 2 subsets defined:

3.4.1 Humoral Serology Subset

All participants in the PP Analysis Set who were tested for HAI, microneutralization (MN) and anti-rS protein serology (ELISA) prior to study vaccination will be included in this subset.

This includes testing for homologous and/or heterologous strains.

3.4.2 Cell-mediated Assay Subset

All participants in the PP Analysis Set who have their CMI response assessed by ICCS and/or ELISpot prior to study vaccination will be included in this subset. CMI assessments are at Days 0, 7, 63 and 182 for all participants for a preselected subset of study sites.

Approximately 50% of all participants will be allocated to the CMI Subset population for the analysis of CMI endpoints. The participants will be chosen based on site location and feasibility of testing.

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.

The Study Deviation Rules Document will be used to classify protocol deviations identified through monitoring activities.

Some PDs may be determined programmatically through the course of the trial. PPD ensures these are reconciled with manually determined PDs in PPD's clinical trial management system. Examples of programmatically-determined PDs are provided in Table .

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

Table 3 Programmatically-Determined Protocol Deviations

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 PPD 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 per the Study Rules Document.

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 safety or secondary immunogenicity outcomes will exclude those participants from the PP analysis set. Prior to unblinding, PPD 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 PPD.

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

- Failure to obtain and file a completely executed and documented informed consent.
- Fraudulent or fabricated data
- Inclusion criteria not met or exclusion criteria met
- Failure to receive, or document receipt of, the study treatment as randomized.
- For inclusion in the PP Analysis Set, failure to provide or to provide out of protocol-specified window, a sample for serologic analysis on Days 28, 56, and 70.
- Administration of the incorrect study vaccine or incorrect volume of vaccine or vaccine impacted by temperature excursion or expired vaccine per treatment arm assigned at Day 0 or Day 56
- Administration of the incorrect study vaccine or incorrect volume of vaccine or vaccine impacted by temperature excursion or expired vaccine per treatment arm assigned at Day 70 (only for Study Vaccine Group O)
- Anytime criteria for premature discontinuation of trial vaccine administration are met but participant was not withdrawn from vaccine administration
- 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 Protocol
    - No routine (non-emergent) vaccines will be allowed until after study Day 70

- No influenza vaccine will be allowed within 2 months prior to first study vaccination until after the last study visit (Day 182).
- No investigational product (drug/biologic/device) within 90 days prior to first study vaccination until after the last study visit (Day 182).
- No chronic administration (defined as more than 14 continuous days) of any immunosuppressant medication within 3 months of first study vaccination until the last study visit (except topical, inhaled, or intranasal steroids or short-term oral steroids with course lasting ≤ 14 days).

4 SUBJECT DISPOSITION

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

The number (percentage) of participants in the Randomized Set, FAS, Safety Analysis Set, and PP Analysis Set who have completed the study up to the time of analysis (Day 70 and EoS) will be summarized by the study vaccine group.

The number (percentage) of participants in the Safety Analysis Set who discontinue the study prior to the time point of analysis (Day 70 and EoS) and the reason for study discontinuation (eg, AE, physician decision, lost to follow-up, site termination by sponsor, etc.) will be presented by the study vaccine group. A listing of all participants who are discontinued will be presented by the study vaccine group, reason for study discontinuation, and day of last study contact. Day of last study contact will be calculated as follows: date of study discontinuation (as recorded on Study Completion eCRF) minus date of Day 0 vaccination.

The number (percentage) of participants in the Safety Analysis Set with treatment discontinuation prior to the time point of analysis (Day 70 and EoS) and the reason for treatment discontinuation (eg, noncompliant with the protocol, SAE, pregnant, receives an approved or deployed SARS-CoV-2 vaccine, etc.) will be presented by the study vaccine group. A listing of all participants with treatment discontinuation will be presented by the study vaccine group, reason for treatment discontinuation, and day of last study contact.

The number (percentage) of participants in the Safety Analysis Set with a major protocol deviation recorded up to time of analysis (Day 70 and EoS) will be summarized by the study vaccine group and protocol deviation category (according to the Study Rules Document provided by CRO). 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 0, 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 0 vaccination, sex, race, ethnicity, height, weight, BMI, child-bearing potential) will be summarized by the study vaccine group on the FAS, Safety Analysis Set, Per Protocol Set, and the subset of subjects analyzed for CMI.

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) measurements recorded at Study Day 0 and derived BMI. Age (years) at the Day 0 vaccination will be calculated as the closest lower integer result of (Date of Study Day 0 – Date of Birth) / 365.25, and will be summarized using the above descriptive statistics.

The number and percentage of participants for Sex (Male, Female), Ethnicity (Hispanic or Latino, not Hispanic or Latino, not reported, unknown), Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other, Not Reported), BMI category will be summarized. If a subject indicates more than one race, the subject may be counted as Mixed Race. BMI categories are:

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

Medical history will be coded using the MedDRA terms. Physical examination diagnoses/abnormalities will be recorded by body system. Baseline medical history recorded on Day 0 (prior to vaccination) will be summarized separately by the study vaccine group and by MedDRA 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 findings will be summarized separately by study vaccine group and by body system.

Baseline anti-NP results will be summarized qualitatively and/or quantitatively by study vaccine group. A breakdown of baseline seropositivity may be summarized by study vaccine group to report the number and percentage of participants having a previous COVID-19 vaccination and/or reporting a previous SARS-CoV-2 infection. In addition, the time between prior exposure to SARS-CoV-2 (either first dose of vaccine or natural infection) and Day 0 may be summarized by study vaccine group using descriptive statistics (i.e. 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 0 and Day 56 by the study vaccine group. The number and percentage of participants who received the study vaccine at Day 70 will only summarized in the study vaccine group O.

6.2 Concomitant Medication

Concomitant medications will include all medications (including any approved or deployed COVID-19 or influenza vaccine) taken by the participant from the time of signing the ICF

through 182 days after the first vaccination (or through the early termination visit if prior to that time). After Day 70, only those concomitant medications taken for any of the following events will be recorded: any MAAEs, SAEs, or AESIs (including PIMMCs).

The number (percentage) of participants who record one or more prior/concomitant medications (including vaccines) recorded on 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 ATC term and standardized medication name.

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

7 ANALYSES ADDRESSING PROTOCOL OBJECTIVES

7.1 Analyses of Primary Endpoint of Safety

The analysis of the primary safety endpoints will be descriptive and based on the Safety Analysis Set. Safety will be summarized by individual study vaccine group (groups A and C will be combined as will be groups H and N) including solicited AEs over 7 days after each of the first and second doses, unsolicited AEs over 70 days after the first dose by MedDRA preferred term, and MAAEs, SAEs, and AESIs over 6 months (approximately 182 days) after first dose. All AEs, including MAEs, SAEs, and AESIs will be tabulated by severity, and relatedness. Missing data will not be imputed.

7.1.1 Solicited Adverse Events

Solicited AEs are reported within 7 days following the Day 0 and Day 56 vaccination with specific verbatim terms reported via an eDiary. These events are considered related to the study vaccine and are collected using a severity rating of 1, 2, 3 or 4 (Mild, Moderate, Severe, or Potentially Life Threatening, respectively), using the maximal severity observed for the specific local and general systemic reactogenicity post-vaccination based on the Modified FDA Toxicity Grading Scale for Clinical Abnormalities (Appendix 2). Notable exceptions include oral temperature and events of injection site redness and swelling which are collected as continuous variables. Oral temperature (fever) will be summarized by severity according to regulatory guidance (**Error! Reference source not found.**Appendix 2), eg, Normal < 38.0ºC, Mild = 38.0 – 38.4ºC, Moderate = 38.5 – 38.9ºC, Severe = 39.0 – 40ºC, Potentially Life Threatening > 40ºC. Redness and swelling will be summarized by severity according to regulatory guidance (**Error! Reference source not found.**Appendix 2), eg, Normal < 2.5cm, Mild = 2.5 – 5cm, Moderate = 5.1 – 10cm, Severe = > 10cm, Potentially Life Threatening will be monitored through the AE eCRF.

The number and percentage (with two-sided exact 95% CIs using the Clopper-Pearson method) of participants reporting solicited injection site and systemic AEs on the eDiary through 7 days after each vaccine dose (within the post-vaccination window of Days 0 - 6) will be summarized by study vaccine group, for each post-vaccination period and overall across both initial doses (including Group O). Worst maximum toxicity grade over 7 days for each reaction and overall

will be reported by study vaccine group. The duration of solicited local and systemic AEs within the 7 day reporting period after each vaccination will also be summarized by the study vaccine group. For each reaction and overall, the number of participants with a solicited AE continuing past Day 6 will be reported.

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

- Summaries of all local (injection site)/systemic reactogenicity AEs by the verbatim terms for the first dosing/the second dosing/post any dosing
- Summaries of all local (injection site)/systemic reactogenicity AEs for any and by severity for the first dosing/the second dosing/post any dosing
- Duration of all local (injection site)/systemic reactogenicity AEs for the first dosing/the second dosing
- Listings of participants with local (injection site)/systemic reactogenicity AEs
- Summaries of participants with local/systemic solicited AEs continuing past Day 6

In addition, between-group difference of proportions of participants experiencing any solicited local (injection site)/systemic AE between groups will be calculated as follows:

- Groups A to N individually after first dose against Groups O and P after first dose
- Groups A to N individually across 2 doses against Groups O and P after first dose
- Groups A to N individually across 2 doses against Group P across 2 doses

Two-sided 95% CIs for the risk differences will be calculated with the method of Miettinen and Nurminen. Sample SAS code is presented below:

```
proc freq data=<solicited_data>;
    tables <arm>*<indicator of occurrence> / missing riskdiff (cl=MN);
run;
```

7.1.2 Unsolicited Adverse Events

Unsolicited adverse events are defined as any adverse events occurring within the 7-day window following vaccination and not specifically solicited in the diary, or any adverse event that occurs outside the 7-day diary solicitation period. All unsolicited AEs of any severity will be collected from the time of first study vaccination through Day 70 (ie, until 14 days after the second vaccination). Any relevant observations made prior to the first dose of study vaccine are to be recorded on the AE eCRF but will not be considered TEAEs and will be reported separately from TEAEs. The time periods for summary of adverse events are described at the end of this section. Summaries for other time periods may also be produced.

Unsolicited AEs will be coded by Preferred term (PT) and System Organ Class (SOC) using the latest version of Medical Dictionary of Regulatory Activities (MedDRA). Unsolicited AEs will be summarized overall and by study vaccine group then by SOC/PT as well as by severity (Mild, Moderate, Severe, or Potentially Life Threatening), and relatedness (not related,

related, not applicable) to the study vaccine. For multiple occurrences of an AE 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. The number and percentage with its corresponding exact 95% CIs of unsolicited AEs will be calculated using Clopper-Pearson method.

An MAAE is defined as an AE that leads to an unscheduled visit to a healthcare practitioner. AESIs include PIMMCs, AEs specific to complications of COVID-19 (listed in **Error! Reference source not found.**), or other potential AEs that may be determined at any time by regulatory authorities as additional information concerning COVID-19 is obtained. All MAAEs and AESIs (including PIMMCs and complications to COVID-19) will be collected from the first study vaccination through Day 182 after first vaccination. An AESI must be reported as if it is an SAE. 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. All SAEs will be collected from signing of informed consent until completion of the EoS.

All MAAEs, any MAAEs related to vaccine, AESIs (including PIMMCs and complications to COVID-19), SAEs, any SAEs related to vaccine through Day 182 after first vaccination will be summarized overall and by the study vaccine group as well as by severity using the provided criteria (Appendix 2 and Appendix 3).

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 AEs (Days 0 - 70)
- Summaries of all unsolicited AEs by MedDRA SOC/PT and severity (Days 0 - 70)
- Summaries of all unsolicited AEs by MedDRA SOC/PT and relationship to study vaccine (Days 0 - 70)
- Summaries of MAAEs, SAEs, and AESIs (including PIMMCs and complications to COVID-19) by MedDRA SOC/PT and relationship to study vaccine (Days 0-70, Days 71-182, Days 0 - 182)
- Listings of all unsolicited AEs including MAAEs, AESIs (including PIMMCs and complications to COVID-19) and SAEs (Days 0-70, Days 71-182, Days 0 - 182)

7.2 Analysis of Secondary Immunogenicity Endpoints (Traditional Approach)

The analysis of secondary immunogenicity endpoints will be descriptive with no formal statistical testing. The PP analysis set will be the primary population for analysis as the results of this population are of primary interest when selecting dose/formulation for further study. 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/concentrations reported below the lower limit of quantification (LLOQ) will be set to half that limit (ie, if LLOQ=10, then 10/2 = 5) for use in computations.

7.2.1 HAI and MN Titers for Influenza Strains

As a secondary objective, serum HAI antibody response (assayed with wild-type VLP reagents) at Day 28 (post-first dose of trial vaccine), Day 56, and Day 70 (post-second dose of trial vaccine) and at other follow-up time points (Days 84 and 182), against 4 vaccine-homologous strains, and at least 1 antigenically drifted A or B strain will be assessed. In addition, neutralizing antibody responses (assayed with wild-type virus) against 4 vaccine-homologous strains, and at least 1 antigenically drifted A or B strain will be conducted. For both homologous and heterologous (ie, antigenically drifted) influenza strains, and for both results arising from HAI assay and MN assay, titer data will be summarized by GMT, GMFR, SCRs and SPRs.

The derived/calculated endpoints of HAI antibody response will include:

- Geometric mean titer (GMT) – defined as the antilog of the mean of the log-transformed HAI titers on Days 0, 28, 56, 70, 84 and 182.
  - HAI GMTs 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.
- $GMFR_{Post/Pre}$ – defined as the within group ratio of post-vaccination to pre-vaccination (Day 0) HAI GMTs, on Days 28, 56, 70, 84 and 182.
  - HAI $GMFR_{Post/Pre}$ for each study vaccine group will be conducted using paired t distribution. A sample SAS code is given below:

```
proc ttest data= HAIdata alpha=0.05;
      by Treatment Visit;
      PAIRED log(HAI_D28)*log(HAI_D0);
run;
```

- HAI GMTR between selected study vaccine groups at post-vaccination time points (adjusted for intergroup variation in baseline [pre-vaccination] titers) and two-sided 95% CI will be calculated on log-transformed titers using the analysis of covariance (ANCOVA) with the study vaccine group and baseline (Day 0) measurement as the covariates under two-sided type I error rate of 0.05. No type I error rate will be adjusted.
  - Groups A-N (experimental vaccine) individually after 1 dose at Day 28 to Group O (reference vaccine) after 1 dose at Day 28
  - Groups A-N (experimental vaccine) individually after 2 doses at Day 70 to Group O (reference vaccine) after 1 dose at Day 28
  - Sample SAS code for GMTR between study vaccine groups is given below:

```
proc mixed data= HAIdata;
      class Treatment;
      model log(HAI) = log(HAI_D0) Treatment;
      lsmeans Treatment/cl diff e alpha=0.05;
```

```
run;
```

- SCR – defined as proportion of participants with either a baseline reciprocal (Day 0) titer of < 10 and a post-vaccination reciprocal titer ≥ 40, or a baseline reciprocal (Day 0) titer of ≥ 10 and a post-vaccination titer ≥ 4-fold higher than the baseline titer as measured on Days 28, 56, 70, 84 and 182.
  - SCR and corresponding 2-sided exact binomial 95% CIs will be calculated using the Clopper-Pearson method with the following sample SAS code:

```
proc freq data=HAIdata noprint;
      by Treatment Visit;
      tables seroconvind / binomial(exact) alpha=.05;
      output out=out1 binomial;

run;
```

- Two-sided 95% CIs of the difference in SCRs in HAI titers for the above cited comparisons of HAI GMTR will be based on the Miettinen and Nurminen method with the following sample SAS code:

```
proc freq data=HAIdata;
      by Visit;
      tables trtarm*scr / missing riskdiff (cl=MN);
run;
```

- SPR – defined as the proportion of participants with a reciprocal HAI titer ≥ 40 on Days 28, 56, 70, 84 and 182.
  - SPR and corresponding 2-sided exact binomial 95% CIs will be constructed similarly using the Clopper-Pearson method.

The derived/calculated endpoints of MN_{50} antibody responses specific for the influenza HA will include the same assessments of GMT, $GMFR_{Post/Pre}$, GMTR, SCR, SCR differences, and SPR as for HAI antibody response.

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

Participants indicating a lab-confirmed episode of influenza prior to the visit being analyzed may be excluded from the calculations. If this is implemented, it will be determined via a review of unsolicited adverse event data.

7.2.2 ELISA (IgG) Concentration and MN_{50} Titers for SARS-CoV-2

Serum (IgG) antibody responses (ELISA) for vaccine homologous SARS-CoV-2 rS antigen and cross-reactive virus variants, if available, will be conducted. For the serum IgG antibody levels specific for the rS antigen(s) as detected by ELISA, the derived/calculated endpoints of IgG antibody response will include: GMEU, GMEUR, $GMFR_{Post/Pre}$, SCR, which will be calculated in manner similar to HAI antibodies described above. Further description of the analyses for GMEUR appear at the end of this section.

MN_{50} antibody responses for vaccine homologous SARS-CoV-2 rS antigen and cross-reactive virus variants, if available, will be conducted. The derived/calculated endpoints of MN_{50}

antibody responses specific for SARS-CoV-2 wild-type will include the same assessments of GMT, $GMFR_{Post/Pre}$, GMTR, SCR as HAI antibody response.

The definition of seroconversion is a post-vaccination concentration/titer ≥ 4-fold higher than baseline. Participants indicating evidence of infection with SARS-CoV-2 prior to the time point analyzed may be excluded from the calculations. This will be determined by examining the anti-NP results taken at Day 70 and/or Day 182. An alternative measure, seroresponse, may be explored which is defined as participants having a value or fold-rise greater than the 95th percentile of values in a reference group, which would be chosen if this analysis is performed and described in the study report.

Between-group GMEUR of IgG and MN antibodies to SARS-CoV-2 will be calculated at post-vaccination time points (adjusted for intergroup variation in baseline [pre-vaccination] values) and two-sided 95% CI will be calculated on log-transformed values using the analysis of covariance (ANCOVA) with the study vaccine group and baseline (Day 0) measurement as the covariates under two-sided type I error rate of 0.05. No type I error rate will be adjusted.

- Groups A-N (experimental vaccine) individually after 1 dose at Day 28 to Group P (reference vaccine) after 1 dose at Day 28
- Groups A-N (experimental vaccine) individually after 2 doses at Day 70 to Group P (reference vaccine) after 2 doses at Day 70

Two-sided 95% CIs of the difference in SCRs for IgG and MN antibodies to SARS-CoV-2 for the above cited comparisons of GMEUR will be based on the Miettinen and Nurminen method with the following sample SAS code:

```
proc freq data=SARSdata;
      by Visit;
      tables trtarm*scr / missing riskdiff (cl=MN);

run;
```

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

7.3 Analysis of Exploratory Immunogenicity Endpoints

CMI responses to the various formulations/regimens in terms of peripheral blood CD4+ T cells which express one or more cytokines or activation markers (e.g. CD40L, INF-gamma, IL-2, TNF-alpha, IL-13) in response to in-vitro stimulation with strain-specific HA or rS will be assessed. Analysis of exploratory CMI response endpoints will be performed on a subset of approximately 50% of all participants chosen based on site location and feasibility of testing at Days 0, 7, 63 and 182 measured by ICCS and/or ELISpot assay. CMI results may be reported as an addendum to the main CSR.

The analysis for CMI response may include:

- Counts and/or proportions at Day 0, 7, 63, and 182 will be summarized by study vaccine, strain, and visit.

- Geometric mean counts (GMC) calculated as the antilog of the mean of the log-transformed counts at Day 0, 7, 63, and 182 will be summarized by study vaccine, strain, and visit.
- Geometric mean fold rise (GMFR) of counts between post-vaccination (Day 7/63/182) and pre-vaccination (Day 0) will be summarized by study vaccine, strain, and visit.
- GMCR – between-group ratio of geometric mean of counts for interested comparisons at Day 7, 63, and 182, adjusted for intergroup variation in baseline [pre-vaccination] counts.
  - The log10 values will be used to construct a 95% CI using the analysis of covariance (ANCOVA) with the study vaccine group and baseline at Day 0 as the covariates

Graphical presentations of the analyses (e.g., boxplots, bar graphs with corresponding 95% CIs, reverse cumulative distribution curves) may be generated.

Further details for data handling of CMI data will be provided by Novavax laboratory scientists at the time of analysis. Examples include LLOQ values for individual cytokines, whether background values need to be subtracted, handling zero or negative counts, and units for reporting.

Immune response to the various formulations/regimens in terms of human angiotensin-converting enzyme 2 (hACE2) inhibition antibodies will be analyzed descriptively in a manner similar to the summaries described for IgG antibody concentration and MN_{50} antibody titers for SARS-CoV-2 (reference Section 7.2.2).

7.4 Analysis of Immunogenicity Endpoint Using the DoE Approach

The study's 12 unique vaccine formulations (excluding reference formulations) arose from a DoE approach with the objective to construct one or more response surface models that can provide information on combination(s) of antigen quantities (both HA and rS) that when combined with 50 μg of Matrix-M1 adjuvant will maximize HAI and anti-S immune responses. The combination(s) identified may or may not be the formulations that are currently being studied. The goal of response surface modelling is to establish the relationship between response and one or more factors, using a set of tools to identify factor settings which optimize response. The results are intended to inform selection of potential dose levels for further study. The modelling exercise will consist of a prospectively established set of analyses and may be followed by further exploration. The SAP defines the prospective set of analyses, whereas further exploratory modelling will be described in the clinical study report.

Day 28 (post single dose) and Day 70 (post 2 doses) immune responses will be the data of primary interest for the regression analysis. Participants in the study are baseline seropositive for SARS-CoV-2 and can be expected to have previously exposure to influenza viruses, so baseline antibody levels for the response parameters are likely to vary and be predictive of response at Days 28/70. Therefore, participants with non-missing Day 28/70 and baseline values in the PP Analysis Set for the responses of interest (Section 7.3.1) will be included in the modeling. In response surface modelling, treatment group is not explicitly designated as an independent variable but are indirectly reflected by factor levels that account for the

amount of each antigen (HA or rS) received. These are treated mathematically as coded continuous quantities ranging from -1 to 1. Participants having a lab-confirmed case of influenza (determined via examination of adverse event reporting) or COVID-19 (determined by anti-NP) between Day 0 and Day 70 may be excluded for the modeling to reduce the extra variability arising from such data points.

To incorporate variation in baseline antibody levels, the individual participant fold-rise in anti-spike and HAI antibody responses at each time point (Table 4) would be used to build predictive model(s). However, examination of the data may reveal that using absolute value is more appropriate, with or without considering the baseline value as a predictor. The starting point is a full model that will includes all main effects, interactions, and quadratic effects.

Table 4 List of Responses for Response Surface Modelling

Response	Transformation	Goal
Fold-rise (or absolute value) of HAI titer to A/Brisbane/02/2018 [H1N1] pdm09 (homologous strain) at Day 28 relative to Day 0	Logarithm	Maximize
Fold-rise (or absolute value) of HAI titer to A/Kansas/14/2017 [H3N2] (homologous strain) at Day 28 relative to Day 0	Logarithm	Maximize
Fold-rise (or absolute value) of HAI titer to B/Maryland/15/2016 [Victoria] at Day 28 relative to Day 0	Logarithm	Maximize
Fold-rise (or absolute value) of HAI titer to B/Phuket/3073/2013 [Yamagata] at Day 28 relative to Day 0	Logarithm	Maximize
Fold-rise (or absolute value) of IgG by ELISA to SARS-CoV-2 rS at Day 28 relative to Day 0	Logarithm	Maximize
Fold-rise (or absolute value) of HAI titer to A/Brisbane/02/2018 [H1N1] pdm09 (homologous strain) at Day 70 relative to Day 0	Logarithm	Maximize
Fold-rise (or absolute value) of HAI titer to A/Kansas/14/2017 [H3N2] (homologous strain) at Day 70 relative to Day 0	Logarithm	Maximize
Fold-rise (or absolute value) of HAI titer to B/Maryland/15/2016 [Victoria] at Day 70 relative to Day 0	Logarithm	Maximize
Fold-rise (or absolute value) of HAI titer to B/Phuket/3073/2013 [Yamagata] at Day 70 relative to Day 0	Logarithm	Maximize
Fold-rise (or absolute value) of IgG by ELISA to SARS-CoV-2 rS at Day 70 relative to Day 0	Logarithm	Maximize

Further exploratory modelling may be performed on cell-mediated immunity (CMI) response measures (e.g.homologous SARS-CoV-2 spike-specific or specific HA T-cell counts), as well as antibody responses tested with different assays (e.g. neutralization titers) or on drift strains. These analyses would be specified in a separate document and described in the clinical study report.

There are 2 factors studied (Table 5)—the nominal amount (in μg) of SARS-CoV-2 rS protein in each dose, and the nominal amount (in μg) of each of four (4) HA strains for influenza strains in each dose.

Table 5 List of Factors in Design of Experiments Approach

Factor (unit)	Role	Lower value	Upper value
SARS-CoV-2 rS (μg)	Continuous	2.5	22.5
HA per strain (μg)	Continuous	5	60

Table 6 shows the planned list of runs identified by the DOE platform within SAS JMP and number of planned replicates per run. The actual number of replicates providing data will be dependent on the enrollment into the study and exclusion of subjects from the PP Analysis Set. Runs 1 and 3, as well as 8 and 14, are identically specified.

Table 6 Planned List of Runs

Run	Replicates	Value for SARS-CoV-2 Factor	Value for HA Factor
1	40	22.5	60
2	40	2.5	10
3	40	22.5	60
4	40	7.5	10
5	40	22.5	10
6	40	7.5	35
7	40	22.5	5
8	40	2.5	60
9	40	7.5	5
10	40	2.5	5
11	40	22.5	35
12	40	2.5	35
13	40	7.5	60
14	40	2.5	60

Factor levels are treated as continuous coded values ranging from -1 to 1 so that each factor contributes equally to predicting the optimal response. The initial full regression model to be run is expressed as:

$$Y = \beta_0 + \beta_1 X1 + \beta_2 X2 + \beta_3 X1X2 + \beta_4 X1^2 + \beta_5 X2^2 + \varepsilon$$

where:

Y is the response
X1 = coded antigen level for each HA flu strain
X2 = coded antigen level for SARS-CoV-2 rS
X1*X2 = interaction term for HA antigen level and SARS-CoV-2 rS antigen level
ε = error term with expected value of 0

SAS JMP will be used to fit a least-squares model for each response indicated in Table XX. Each run's replicate values may or may not be averaged across the subjects in the PP Analysis Set to determine the independent Y value for the run. An examination of the data will guide the decision and it will be documented in the report. Baseline measurement for each replicate may be included as covariate if no averaging is performed for a run's replicates. The initial full model will be run and significance of each term examined. A p-value <0.05 indicates that a term is significant. Non-significant terms will be removed and the resulting reduced model (for each response) will be fitted for exploration with a Predication Profiler tool. Desirability functions (ranging from 0 for lowest level to 1 for highest level) will be used to identify factor settings that optimize the set of responses. Weighting for each response may be considered. Factor setting(s) that lead to the highest overall desirability will be the level of HA and rS that optimize responses in Table XX.

As a parallel analysis, SAS PROC RSREG will be used to run a response surface model that uses the dataset without first averaging the results of each run across replicates nor incorporating the baseline measurement into a fold-rise (i.e. use the data as-is). In this model, Y would be set as the antibody response value at the time point of interest, with BL being the corresponding measurement at Day 0. X1 and X2 have the same definition as the when the model is fitted within SAS JMP.

Example SAS code:

```
PROC RSREG DATA=X;
MODEL Y=BL X1 X2 / LACKFIT COVAR=1;
RUN;
```

The fit of the model is to be assessed by examining the p-value from the lack-of-fit test and plots of residuals for each factor. Significance of main, quadratic and interaction effects will also be assessed and reported.

The canonical analysis results from PROC RSREG provide information on the shape of the response surface. A maximum point is identified on the response surface by all eigenvalues being negative (a second order derivative test).

8 ADDITIONAL ANALYSES

8.1 Vital Signs

Vital sign measurements at all visits include temperature (oral or via forehead/ear reader), pulse rate, diastolic and systolic blood pressure (after participant is seated for at least 5 minutes), respiratory rate, and oxygen saturation. Temperature will be recorded and graded during general systemic reactogenicity evaluation. The other vital signs measurements will be recorded as

continuous variables. The measurement for baseline is the last set of vital signs taken immediately prior to first dose.

Descriptive statistics for vital signs will be presented by study vaccine group for all participants in the Safety Analysis Set including absolute means and SDs, minimum, maximum.

8.2 Physical Examinations

Physical examinations performed at post-baseline scheduled visits will be summarized by study vaccine group and by body system. For each body system examined, the number and percentage of participants with normal/abnormal results will be reported. The calculation of abnormal results will also be broken out by whether the abnormal result was considered clinically significant or not.

9 CONDUCT OF ANALYSES

As all analyses are descriptive, there are no interim analyses planned that require adjustment to Type I error.

After all participants have completed Day 70, and their data are cleaned, an analysis of the safety primary endpoints through Day 70 and relevant secondary/exploratory immunogenicity endpoints (HAI, MN_{50}, IgG) through Day 70 and possibly available CMI through Day 63. Immunogenicity Data through Day 70 will also be used in the response surface modeling covered under the exploratory analysis. At this point, members of the Novavax Biostatistics team will be unblinded as described in section 1.4.

After all participants have completed through Day 182 after first vaccination, and their data are cleaned, an analysis of all primary safety endpoints through Day 182 and relevant secondary endpoints/exploratory endpoints (HAI, MN_{50}, IgG and CMI) through Day 182 will be conducted.

10 COMPUTER METHODS

With the exception of DoE modelling, statistical analyses will be performed using SAS® version 9.4 or higher in a Windows environment. DoE modelling will primarily be performed using JMP Pro version 16 in a Windows environment, with PROC RSREG being implemented in SAS.

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 concentration values.

The individual HAI titer values, immunogenicity (MN_{50}) titer values and IgG concentration 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 lab or CRO as part of the data transfer.

Medical history and AEs will be coded using MedDRA Version 24.1.

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

Table 7 Decimal Numbers for Parameters

Parameter	Number of Decimal
Number of participants (e.g., N, N1, N2)	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
SPR (%), SCR (%), their corresponding 95% CIs	1

Note: For analysis of exploratory CMI response, up to 5 decimal numbers will be presented depending on number of significant digits for each parameter.

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.

11.2 Adjustments for Covariates

Comparison of GMTR/GMEUR between the study vaccine groups will be adjusted for pre-vaccination titer.

11.3 Multiple Comparisons/Multiplicity

No multiplicity adjustment will be applied for the secondary immunogenicity 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).

Vaccination with an approved or deployed SARS-CoV-2 vaccine alone will not require withdrawal from the study; and such participants will be encouraged to continue their participation.

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, are discontinued from further study vaccination, 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

In general, there will be no substitutions made to accommodate missing data points. All data recorded on the eCRF will be included in data listings that will accompany the CSR. Partially recorded dates for on-study events should result in query to the site before undertaking the data handling steps below.

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 0 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 0 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 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.

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

As a note, randomization scheme has been updated to reflect stratification by age group, and not by site.

There are 2 per-protocol analysis sets instead of the 3 stated in the protocol.

50% of subjects will have PBMCs collected instead of 5% stated in protocol.

There are multiple response surface models being constructed for a set of antibody responses, rather than using a mean of values among anti-spike and HAI values.

Analyses of unsolicited adverse events reflect that the primary data collection period of such data is through Day 70 (14 days after Dose 2).

13 REFERENCES

Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Biologics Evaluation and Research (US). Guidance for industry: Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. September 2007. Available from: https://www.fda.gov/media/73679/download

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14 APPENDIX

Appendix 2 Schedule of Events for Study 2019nCoV-ICC-E-101

Study Day:	0	7	28	56	63	70	84	182[8]
Window (days):	0	+ 3	+ 3	+ 5	+ 3	+ 5	+ 5	± 14
Study Visit:	1	2	3	4	5	6	7	8
Informed consent	X							
Medical history	X							
Inclusion/exclusion criteria, including determination of baseline seropositivity to SARS-CoV-2 based on SARS-CoV-2 vaccination documentation or history of prior SARS-CoV-2 infection	X							
Randomization	X							
Demographics	X							
Prior/concomitant medications	X	X	X	X	X	X	X[11]	X[11]
Vital signs measurements	X[1]	X	X	X[1]	X	X	X	X
Urine pregnancy test	X			X		X[12]		
Physical examination (at baseline and as required thereafter)[9]	X	X	X	X	X	X	X	X
Vaccination	X[2]			X[5]		X[10]		
Reactogenicity / Participant Diary Completion	X[3]	X		X[4,5]	X			
Blood sampling for SARS-CoV-2 (anti-NP) antibodies	X[6]					X		X
Blood sampling for SARS-CoV-2 immunogenicity (ELISA), HAI serology, and influenza virus MN_{50} assay (testing performed at Novavax)	X[6]		X	X[6]		X	X	X
Blood sampling for SARS-CoV-2 MN_{50} assay	X		X	X		X	X	X
Whole blood sampling and PBMC harvest for SARS-CoV-2 spike-specific T cell counts at a pre-specified subset of sites[7]	X	X			X			X
Unsolicited AEs	X	X	X	X	X	X		
MAAEs	X	X	X	X	X	X	X	X
SAE	X	X	X	X	X	X	X	X
AESIs (including PIMMCs)	X	X	X	X	X	X	X	X

ELISA = enzyme-linked immunosorbent assay; EoS = End of Study; HAI = hemagglutination inhibition; IFNγ = interferon gamma; IL-2 = interleukin-2; MAAE = medically attended adverse events; MN = microneutralization; NP = nucleoprotein; PBMC = peripheral blood mononuclear cells; PCR = polymerase chain reaction; PIMMC = potential immune-mediated medical conditions; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; Th1 = Type 1 T helper; Th2 = Type 2 T helper; TNFα = tumor necrosis factor alpha.

1. Vital signs to be captured pre-vaccination and between 30 to 60 minutes post-vaccination.
2. Participants should be free of acute illness (defined as the presence of a moderate or severe illness in the clinical judgment of the investigator) with or without fever, or an oral temperature ≥ 38°C in order to receive the test article injection. Participants presenting with an acute illness on screening/Day 0 may return to the trial site within the next 7 days to receive their injection provided symptoms have resolved.
3. Starting on the first vaccination day (Day 0) and for 6 days thereafter (Day 0 through Day 6, inclusive), participants will maintain diaries for daily recording of their body temperature and any AE spontaneously offered (reactogenicity).
4. Starting on the second vaccination day (Day 56) and for 6 days thereafter (Day 56 through Day 62, inclusive), participants will maintain diaries for daily recording of their body temperature and any AE spontaneously offered (reactogenicity).
5. Participants presenting with an acute illness on Day 56 may return to the trial site within the next 7 days to receive their second vaccination. If a participant has experienced any AEs/AESI/SAEs between trial Days 0 and 56, the Day 56 vaccination may be administered or delayed for up to 7 days based on the investigator's discretion.
6. Day 0 prior to vaccination.
7. Including IL-2, TNFα, CD40L, and IFNγ.

8. EoS.
9. After physical examination at baseline determines eligibility, subsequent physical examination assessments are symptom directed as triggered by AE or symptom reports.
10. In order to receive a complete 2-dose series of COVID-19 vaccine, participants from treatment group O will receive a third dose of vaccine consisting of 5 µg SARS-CoV-2 rS nanoparticle vaccine and 50 µg Matrix-M1 at Day 70. Note that because Vaccine Group O is the only treatment group receiving a vaccine at Day 70, Vaccine Group O participants and site staff will be unblinded to participant's treatment status from Day 70 onwards. The Sponsor recognizes this partial unblinding and assesses it as having minor impact to the data.
11. After Day 70, only those concomitant medications taken for any of the following events will be recorded: any MAAEs, SAEs, or AESIs (including PIMMCs).
12. Participants in Vaccine Group O who are women of childbearing potential will have a urine pregnancy test performed at the Day 70 visit prior to dosing.

Appendix 2 Toxicity Grading Scale for Clinical Abnormalities (Local and General Systemic Reactogenicity, and Vital Signs

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: **Error! Reference source not found.**

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 signs 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).

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Appendix 3 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 (**Error! Reference source not found.**). Note that this regulatory request is not specific to Novavax's qNIV or SARS-CoV-2 rS or Matrix-M1 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.

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.
Vasculitides:	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.

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.

AEs specific to COVID-19 are listed below (**Error! Reference source not found.**). The list is not intended to be exhaustive, nor does it exclude the possibility that other diagnoses may be AESI.

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: AIDS = acquired immune deficiency disease syndrome; ARDS = acute respiratory distress syndrome; COVID-19 = coronavirus disease 2019; DAIDS = Division of AIDS, NIAID, NIH; MedDRA = Medical Dictionary for Regulatory Activities; NIAID = National Institutes of Allergy and Infectious Diseases; NIH = National Institutes of Health.

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 (**Error! Reference source not found.**).
2. Cytokine release syndrome related to COVID-19 infection is a disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath (**Error! Reference source not found.**).