TITLE PAGE

A Phase 3, Randomized, Observer-Blinded, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Immunogenicity of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine (SARS-CoV-2 rS) with Matrix-M1™ Adjuvant in Adult Participants ≥ 18 Years

Protocol Number:	2019nCoV-301
Amendment Number:	Version 3.0
Test Product:	SARS-CoV-2 rS with Matrix-M1™ Adjuvant
Indication:	Prevention of COVID-19 caused by SARS-CoV-2
Development Phase:	Phase 3
Sponsor:	Novavax, Inc. 21 Firstfield Road Gaithersburg, MD 20878 United States
IND:	022430
EudraCT:	2020-004042-11
Approval Date:	16 November 2020

SPONSOR SIGNATURE PAGE

PROTOCOL TITLE: A Phase 3, Randomized, Observer-Blinded, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Immunogenicity of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine (SARS-CoV-2 rS) with Matrix-M1™ Adjuvant in Adult Participants ≥ 18 Years

PROTOCOL NUMBER: 2019nCoV-301

Novavax, Inc.

[redacted] Clinical Operations | Date (day/month/year)

[redacted] Clinical Development, [redacted] | Date (day/month/year)

1 GENERAL INFORMATION

A Phase 3, Randomized, Observer-Blinded, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Immunogenicity of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine (SARS-CoV-2 rS) with Matrix-M1™ Adjuvant in Adult Participants ≥ 18 Years

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Clinical Research Organization:	ICON Clinical Research, Ltd. [redacted]
Sponsor Signatories:	[redacted] Clinical Operations Novavax, Inc. 21 Firstfield Road Gaithersburg, MD 20878 United States
Sponsor Medical Expert:	[redacted] Clinical Development, Novavax, Inc. 21 Firstfield Road Gaithersburg, MD 20878 United States

2 STUDY SYNOPSIS

<table>
<tr><td colspan="2">Name of Sponsor/Company:
Novavax, Inc.</td></tr>
<tr><td colspan="2">Name of Product:
SARS-CoV-2 rS</td></tr>
<tr><td colspan="2">Name of Active Ingredient:
SARS-CoV-2 rS + Matrix-M1 adjuvant</td></tr>
<tr><td colspan="2">Title of Study:
A Phase 3, Randomized, Observer-Blinded, Placebo-Controlled Study to Evaluate the Efficacy, Safety and Immunogenicity of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine (SARS-CoV-2 rS) with Matrix-M1™ Adjuvant in Adult Participants ≥ 18 Years</td></tr>
<tr><td colspan="2">Principal Investigator:
This is a multicenter study.</td></tr>
<tr><td colspan="2">Study Centers:
Approximately 125 study sites across North America and globally, if needed</td></tr>
<tr><td>Planned Study Period:
Oct 2020 to 2022</td><td>Development Phase:
Phase 3</td></tr>
<tr><td>Objectives:</td><td>Endpoints:</td></tr>
<tr><td>Primary Objective:
• To evaluate the efficacy of a primary 2-dose regimen of SARS-CoV-2 rS adjuvanted with Matrix-M1 compared to placebo against polymerase chain reaction (PCR)-confirmed symptomatic coronavirus disease 2019 (COVID-19) illness diagnosed ≥ 7 days after completion of the second vaccination in adult participants ≥ 18 years of age.</td><td>Primary Endpoint:
First episode of PCR-positive nasal swab and ≥ 1 of symptomatic mild, moderate, or severe COVID-19, where severity is defined as:
Mild COVID-19 (≥ 1 of the following):
• Fever (defined by subjective or objective measure, regardless of use of anti-pyretic medications)
• New onset cough
• ≥ 2 additional COVID-19 symptoms:
o New onset or worsening of shortness of breath or difficulty breathing compared to baseline.
o New onset fatigue.
o New onset generalized muscle or body aches.
o New onset headache.
o New loss of taste or smell.
o Acute onset of sore throat, congestion or runny nose.
o New onset nausea, vomiting or diarrhea.
OR Moderate COVID-19 (≥ 1 of the following):
• High fever (≥ 38.4°C) for ≥ 3 days (regardless of use of anti-pyretic medications, need not be contiguous days).
• Any evidence of significant lower respiratory tract infection (LRTI):
o Shortness of breath (or breathlessness or difficulty breathing) with or without exertion (greater than baseline).
o Tachypnea: 20 to 29 breaths per minute at rest.
o SpO_2: 94% to 95% on room air.
o Abnormal chest X-ray or chest computerized tomography (CT) consistent with pneumonia or</td></tr>
</table>

	LRTI. • Adventitious sounds on lung auscultation (eg, crackles/rales, wheeze, rhonchi, pleural rub, stridor). **OR Severe COVID-19 (≥ 1 of the following):** • Tachypnea: ≥ 30 breaths per minute at rest. • Resting heart rate ≥ 125 beats per minute. • SpO_2: ≤ 93% on room air or PaO_2/FiO_2 < 300 mmHg. • High flow oxygen (O_2) therapy or non-invasive ventilation (NIV)/non-invasive positive pressure ventilation (NIPPV) (eg, continuous positive airway pressure [CPAP] or bilevel positive airway pressure [BiPAP]). • Mechanical ventilation or extracorporeal membrane oxygenation (ECMO). • One or more major organ system dysfunction or failure to be defined by diagnostic testing/clinical syndrome/interventions, including any of the following: o Acute respiratory failure, including acute respiratory distress syndrome (ARDS). o Acute renal failure. o Acute hepatic failure. o Acute right or left heart failure. o Septic or cardiogenic shock (with shock defined as systolic blood pressure [SBP] < 90 mm Hg OR diastolic blood pressure [DBP] < 60 mm Hg). o Acute stroke (ischemic or hemorrhagic). o Acute thrombotic event: acute myocardial infarction (AMI), deep vein thrombosis (DVT), pulmonary embolism (PE). o Requirement for: vasopressors, systemic corticosteroids, or hemodialysis. • Admission to an intensive care unit (ICU). • Death.
Key Secondary Objective: • To evaluate the efficacy of a primary 2-dose regimen of SARS-CoV-2 rS adjuvanted with Matrix-M1 compared to placebo against PCR-confirmed moderate-to-severely symptomatic COVID-19 illness diagnosed ≥ 7 days after completion of the second vaccination in adult participants ≥ 18 years of age.	**Key Secondary Endpoint:** First episode of PCR-positive nasal swab **and** ≥ 1 moderate or severe COVID-19 as defined under the primary endpoint.

Secondary Objectives:	Other Secondary Endpoints:
• To assess vaccine efficacy (VE) against ANY symptomatic SARS-CoV-2 infection. • To assess VE according to race and ethnicity. • To assess VE in high-risk adults versus non-high-risk adults (high-risk is defined by age ≥ 65 years with or without co-morbidities or age < 65 years **with** co-morbidities [eg, obesity (body mass index [BMI] > 30 kg/m^2), chronic kidney or lung disease, cardiovascular disease and diabetes mellitus type 2] and/or by life circumstance [living or working conditions involving known frequent exposure to SARS-CoV-2 or to densely populated circumstances (eg, nursing homes, factory or meat packing plants, healthcare providers, etc)]). • To describe the humoral immune response to vaccine in terms of neutralizing antibody to SARS-CoV-2 for all Immunogenicity Population Participants, and for subsets with and without prior SARS-CoV-2 exposure determined by detectable anti-nucleoprotein (NP) antibodies at baseline. • To assess the immune response to vaccine by immunoglobulin G (IgG) antibody to SARS-CoV-2 S protein and human angiotensin-converting enzyme 2 (hACE2) inhibiting antibodies at Day 35 and Month 3 for all Immunogenicity Population participants, and for subsets with and without prior SARS-CoV-2 exposure determined by detectable anti- NP antibodies at baseline. • To assess the durability of immune response (IgG antibody to SARS-CoV-2 S protein, hACE2 inhibition, and microneutralization [MN]) at 6, 12, 18 and 24 months after last vaccination for all Immunogenicity Population participants, and for subsets with and without detectable anti-NP antibodies at baseline. • To describe and compare the safety experience for the vaccine versus placebo in adult participants ≥ 18 years of age based on solicited short-term reactogenicity by toxicity grade for 7 days following each vaccination (Days 0 and 21). • To assess overall safety through Day 49 (28 days after second vaccination) and to compare vaccine versus placebo for all unsolicited AEs and medically attended adverse events (MAAEs). • To assess the frequency and severity of MAAEs attributed to vaccine, adverse events of special interest (AESIs), or serious adverse events	• ANY symptomatic SARS-CoV-2 infection, defined as: PCR-positive nasal swab **and** ≥ 1 of any of the following symptoms: o Fever. o New onset cough. o New onset or worsening of shortness of breath or difficulty breathing compared to baseline. o New onset fatigue. o New onset generalized muscle or body aches. o New onset headache. o New loss of taste or smell. o Acute onset of sore throat, congestion or runny nose. o New onset nausea, vomiting or diarrhea. • Neutralizing antibody titers from Immunogenicity Population at Days 0, 35 and Month 3. • Serum IgG levels to SARS-CoV-2 S protein, hACE2 inhibition titers from Immunogenicity Population at Days 0, 35 and Month 3. • Serum IgG levels to SARS-CoV-2 S protein, MN and hACE2 inhibition titers from Immunogenicity Population at Months 6, 12, 18 and 24. • Description of course, treatment and severity of COVID-19 reported after a PCR-confirmed case via the Endpoint Form. • Reactogenicity incidence and severity (mild, moderate or severe) recorded by all participants on their electronic patient-reported outcome diary application (eDiary) on days of vaccination and subsequent 6 days (total 7 days after each vaccine injection). o Reactogenicity endpoints include injection site reactions: ▪ Pain. ▪ Tenderness. ▪ Erythema. ▪ Swelling/induration. o Systemic reactions: ▪ Fever. ▪ Malaise. ▪ Fatigue. ▪ Arthralgia. ▪ Myalgia. ▪ Headache. ▪ Nausea/vomiting. • Incidence and severity of MAAEs through Day 49. • Incidence and severity of unsolicited AEs through Day 49. • Incidence and severity of MAAEs attributed to study vaccine, SAEs and AESIs through Month 12.

(SAEs) through the end of study (EoS) and to compare vaccine versus placebo. • To assess all-cause mortality in vaccine versus placebo recipients. • To describe the severity and course of COVID-19 in vaccine versus placebo recipients in terms of healthcare requirements, utilization and medical assessments. • To assess the proportion of participants (vaccine versus placebo recipients) with SARS-CoV-2 infection determined by anti-SARS-CoV-2 NP antibodies, including specifically asymptomatic infection, across the 2 years of study follow-up. • To assess the VE against SARS-CoV-2 infection determined by anti-SARS-CoV-2 NP antibodies, regardless of whether the infection was symptomatic.	• Incidence and severity of SAEs, MAAEs attributed to study vaccine and AESIs during Month 12 through the EoS. • Death due to any cause. • Data points to be collected for healthcare requirements, utilization and medical assessments from participants who become ill on study will be defined in a separate substudy protocol. • Antibodies to SARS-CoV-2 NP at Days 0 and 35, or Months 3, 6, 12, 18 and 24 will be used to determine natural infection and to determine the incidence of asymptomatic infection acquired during study follow-up. • Antibodies to SARS-CoV NP, regardless of whether the infection was symptomatic.
Exploratory Objectives: • To assess cell-mediated response: o Type 1 T helper (Th1) or Type 2 T helper (Th2) predominance. • To contribute to a larger cross-study National Institutes of Health (NIH) effort to define correlates of risk and protection against SARS-CoV-2 infection and disease. • To assess impact of vaccination on nasal viral load in nasal swabs of participants who develop symptoms of possible COVID-19. • To describe sequences of the genetic material from SARS-CoV-2 viruses detected in COVID-19 cases to evaluate possible viral mutations that may be associated with breakthrough infections.	**Exploratory Endpoints:** • Th1 or Th2 responses, eg, interleukin [IL]-2, IL-4, IL-5, IL-13, tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ) in whole blood and/or harvested peripheral blood mononuclear cell (PBMCs). • Serum samples from a designated subset of up to approximately 4,500 Immunogenicity Population participants (non-overlapping with protocol designated Immunogenicity Population) to be transferred to National Institute of Allergy and Infectious Diseases (NIAID) for testing and analysis to determine correlates of risk and protection. Endpoints will be described in a separate statistical analysis plan developed by external statistics groups (eg, COVID-19 Prevention Network [CoVPN], Operation Warp Speed [OWS]). • Quantitative PCR tests may be performed on nasal swabs collected from this trial to assess whether vaccination impacts viral shedding. • Next-generation sequencing of viral genomes detected in nasal swabs tested by PCR. These data are intended for future assessment across multiple clinical trials and for future publication. These data are not intended for initial regulatory submissions.
Study Design: This is a Phase 3, randomized, observer-blinded, placebo-controlled study to evaluate the efficacy, safety and immunogenicity of SARS-CoV-2 rS with Matrix-M1 adjuvant in adult participants ≥ 18 years of age. Participants will be stratified by age group, and enrollment will occur concurrently within the 2 age strata, 18 to 64 years and ≥ 65 years. The study will be a multicenter, global study with countries selected based on the expected COVID-19 epidemiology and healthcare system characteristics. At least 25% of the study population is intended to be in the ≥ 65 years age group. Most study participants are expected to be enrolled in the United States (US). **Prioritization will be given to enrollment of individuals at high risk for COVID-19 by virtue of Black/African American or Native American race, Latinx ethnicity, co-morbid conditions (eg, obesity [BMI > 30 kg/m^2], chronic kidney or lung disease, cardiovascular disease and diabetes mellitus type 2) and life circumstances (living or working conditions involving known frequent exposure to SARS-CoV-2 or to densely populated circumstances [eg, nursing homes, factory or meat packing plants, healthcare providers, etc]).** (See Section	

8.6 Recruitment and Retention for guidelines with respect to high-risk characteristics.)

Study vaccination regimens will comprise 2 intramuscular (IM) injections (Day 0 and Day 21 + 7 days), preferably in alternating deltoids, with the trial vaccine assigned in a full dose injection volume of 0.5 mL. The dose level selected for evaluation is 5 µg SARS-CoV-2 rS adjuvanted with 50 µg Matrix-M1 based on optimal safety and immunogenicity observed in nonclinical and early clinical data. All vaccinations will be administered on an outpatient basis by qualified vaccine administrators in a way to maintain the blind as described in the Pharmacy Manual. Unblinded product will be managed by unblinded study site personnel who may administer study vaccine, if qualified to do so, but will not otherwise be involved in the study procedures or observations of participants.

Solicited AEs of reactogenicity, all subsequent AEs and COVID-19 symptomatology will be collected via participant reporting in the eDiary utilizing a smartphone application. Participants who do not possess an appropriate device will be provided a device compatible with study requirements. All participants will be trained on the use of these applications at the initiation of the study (Day 0), and a Help Desk will be available 24 hours 7 days a week (24/7) for technical issues. For data entry issues, participants should contact the study site.

Overall safety assessments from Day 0 through the first 12 months of follow-up post final vaccination will include participant-recorded solicited (local and systemic reactogenicity) events through 7 days following each vaccination; unsolicited AEs and MAAEs through Day 49; and MAAEs attributed to vaccine, AESIs, SAEs and investigator-assessed targeted physical examination findings, including vital sign measurements through Month 12. During the second 12 months of follow-up post final vaccination, participants will be queried monthly for MAAEs attributed to study vaccine, AESIs and SAEs.

Blood samples for serologic assessments (anti-NP antibodies, IgG antibody to SARS-CoV-2 S protein, MN, and hACE2 inhibition) will be collected from all participants before the first vaccination and at selected subsequent time points. Testing will be performed on a subset of collected sera from the Immunogenicity Population of up to approximately 1,200 participants from the active and placebo treatment groups that appropriately represent the study population in both age categories and in both countries designated at random by Novavax Biostatisticians who are blinded to treatment assignment. Participants who test positive for COVID-19 anti-NP antibodies and/or PCR-positive nasal swab at baseline, indicating previous SARS-CoV-2 infection, will have SARS-CoV-2 S protein immune responses analyzed, but will not contribute to the primary immunogenicity or efficacy analyses. Results from the anti-NP positive and/or PCR-positive nasal swab participants will be assessed and reported separately. Whole blood samples for PBMC will be collected from a small subset of participants (< 100) representing both age strata and reasonably reflecting the demographic subgroups enrolled at study site(s) with the capacity to isolate PBMCs. These cells will be evaluated for cell-mediated immune responses to vaccine.

Participants will be provided with an oral thermometer on Day 0 and instructed to monitor their body temperature daily throughout the first 12 months of the study and to record temperature and any other relevant symptoms daily in their eDiary (see Section 10.4.3 for details). Participants who are noted during regular monitoring of the eDiary entries to not have reported temperature and symptoms for ≥ 7 days will be contacted by phone to assess clinical status and maintain engagement in the study.

Starting on Day 4, throughout the first 12 months of the study, when fever or other specified symptoms (see Table 3 for symptoms suggestive of COVID-19) are reported in the eDiary for at least 2 consecutive days for the same symptom, participants will be directed via the eDiary to begin nasal self-swabbing for PCR testing within 3 days of symptom onset at home for a total of 3 days and to initiate daily completion of the InFLUenza Patient-Reported Outcome (FLU-PRO) symptom reporting instrument for 10 days after COVID-19 symptom onset or until the participant experiences 2 consecutive asymptomatic days. Participants will be instructed at their enrollment visit on the methods of nasal self-swabbing for COVID-19 and completion of the FLU-PRO symptom reporting instrument. In addition, the eDiary will alert the study site to contact the participant to schedule the in-person Unscheduled Acute Illness Visit.

After the first day of home nasal swabbing, repeat nasal self-swabs should be obtained daily for a total of 3 days to ensure capture of intermittent shedding. The self-swabs obtained by the participant should be maintained according to directions provided in the 3-swab kit, and the designated courier should be contacted to pick up the kit for shipping to the central lab, as directed.

At the in-person Unscheduled Acute Illness Visit, participants will be queried regarding AE symptoms, concomitant medications taken for these symptoms, undergo a targeted physical examination (to include O_2 saturation), if indicated, and have obtained by the study personnel a medically attended nasal swab, a blood sample for serologic testing and be trained on the use of the portable pulse oximeter that they will take home with them.

Medically attended swabs collected at the Unscheduled Acute Illness Visit will be processed at the study site according to established procedures as described in the Laboratory Manual.

Completion of the FLU-PRO reporting instrument and oxygen (O_2) saturation (at rest and following mild exercise, defined as walking around the room for 1 minute) will be captured daily in the eDiary for 10 days after COVID-19 symptom onset or until the participant experiences 2 consecutive asymptomatic days.

Study participants whose home nasal self-swab and/or medically attended nasal swabs are confirmed at the central laboratory to be PCR-positive for SARS-CoV-2 at the Unscheduled Acute Illness Visit will be contacted by the study site to arrange an Unscheduled Convalescent Visit. The Unscheduled Convalescent Visit will occur approximately 1 month (or as soon thereafter, as feasible) after the onset of the PCR-confirmed case of COVID-19 at the Unscheduled Acute Illness Visit to assess status of AEs, record the clinical course of the disease on the Endpoint Form and obtain a blood sample for convalescent serologic testing. Pulse oximeters should be returned to the study site at this visit.

The study will consist of a screening period (up to 30 days prior to Day 0); vaccination days (Days 0 and 21 + 7 days); outpatient study visits on Days 0, 21 (+ 7 days), 35 (+ 7 days), and Month 3 (+ 15 days) and at 6 months (± 15 days) after the last vaccination. Additional study visits for blood draws will occur at 12 (± 15 days), 18 (± 30 days) and 24 months (± 30 days) after the last vaccination. In addition to the aforementioned Unscheduled Acute Illness and Unscheduled Convalescent Visits, an Unscheduled General Visit may be conducted by study personnel in the event of a general medical issue other than COVID-19 symptomatology, if needed. An EoS visit will be recorded for all study participants at approximately 24 months (± 30 days) after their last vaccination or at their last visit on study. Should participants decide to terminate early, an EoS telephone visit will occur to collect the maximum safety data and blood sample, if possible. All study participants will be encouraged to continue in follow-up for safety and reported COVID-19 cases.

This protocol has extensive safety monitoring in place. Safety is monitored daily by the ICON Medical Monitor, Novavax Pharmacovigilance and Safety Surveillance Physicians, and routinely by the 2019nCoV-301 Protocol Safety Review Team (PSRT). In addition, an independent Data and Safety Monitoring Board (DSMB) periodically reviews study data, including unblinded study data if/when needed.

If this vaccine or another is demonstrated to be safe and efficacious and approved by regulatory authorities, participants for whom the new vaccine is recommended and available will be counseled with respect to their options. These participants may be offered the opportunity to be unblinded so that those who received placebo may be offered the Novavax vaccine or another product, as appropriate, outside the protocol procedures. Participants who are unblinded and receive an active vaccine in this manner will be censored in the final analysis at the time of unblinding but will be strongly encouraged to remain in safety follow-up as defined in this protocol.

Number of Participants:

It is planned to enroll up to approximately 30,000 participants.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Inclusion Criteria

Each participant must meet all of the following criteria to be enrolled in this study:

1. Adults ≥ 18 years of age at screening who, by virtue of age, race, ethnicity or life circumstances, are considered at substantial risk of exposure to and infection with SARS-CoV-2. (See Section 8.6, Recruitment and Retention for guidelines with respect to high-risk characteristics.)
2. Willing and able to give informed consent prior to study enrollment and to comply with study procedures.
3. Participants of childbearing potential (defined as any participant who has experienced menarche and who is NOT surgically sterile [ie, hysterectomy, bilateral tubal ligation, or bilateral oophorectomy] or postmenopausal [defined as amenorrhea at least 12 consecutive months]) must agree to be heterosexually inactive from at least 28 days prior to enrollment and through 3 months after the last vaccination OR agree to consistently use a medically acceptable method of contraception from at least 28 days prior to enrollment and through 3 months after the last vaccination.
4. Is medically stable, as determined by the investigator (based on review of health status, vital signs [to include body temperature], medical history, and targeted physical examination [to include body weight]). Vital signs must be within medically acceptable ranges prior to the first vaccination.
5. Agree to not participate in another SARS-CoV-2 prevention trial during the study follow-up.

Exclusion Criteria

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

1. Unstable acute or chronic illness. Criteria for unstable medical conditions include:
   a. Substantive changes in chronic prescribed medication (change in class or significant change in dose) in the past 2 months.
   b. Currently undergoing workup of undiagnosed illness that could lead to diagnosis of a new condition.

   Note: Well-controlled human immunodeficiency virus [HIV] with undetectable HIV ribonucleic acid [RNA < 50 copies/mL] and CD4 count > 200 cells/µL for at least 1 year, documented within the last 6 months, is NOT considered an unstable chronic illness.
2. Participation in research involving an investigational product (drug/biologic/device) within 45 days prior to first study vaccination.
3. History of a previous laboratory-confirmed diagnosis of SARS-CoV-2 infection or COVID-19.
4. Received influenza vaccination or any other adult vaccine within 4 days prior to or within 7 days after either study vaccination.
5. Autoimmune or immunodeficiency disease/condition (iatrogenic or congenital) requiring ongoing immunomodulatory therapy that is judged to cause significant immunocompromise.
   NOTE: Stable endocrine disorders (eg, thyroiditis, pancreatitis), including stable diabetes mellitus with no history of diabetic ketoacidosis) are NOT excluded.
6. Chronic administration (defined as > 14 continuous days) of immunosuppressant, systemic glucocorticoids, or other immune-modifying drugs within 90 days prior to first study vaccination.
   NOTE: An immunosuppressant dose of glucocorticoid is defined as a systemic dose ≥ 20 mg of prednisone per day or equivalent. The use of topical, inhaled, and nasal glucocorticoids is permitted. Topical tacrolimus and ocular cyclosporin are permitted.
7. Received immunoglobulin, blood-derived products, or immunosuppressant drugs within 90 days prior to first study vaccination.
8. Active cancer (malignancy) on chemotherapy that is judged to cause significant immunocompromise within 1 year prior to first study vaccination (with the exception of malignancy cured via excision, at the discretion of the investigator).
9. Any known allergies to products contained in the investigational product.
10. Participants who are breastfeeding, pregnant or who plan to become pregnant within 3 months following last study vaccination.
11. Any other condition that, in the opinion of the investigator, would pose a health risk to the participant if enrolled or could interfere with evaluation of the trial vaccine or interpretation of study results.
12. Study team member or first-degree relative of any study team member (inclusive of Sponsor, and study site personnel involved in the study).
13. Current participation in any other COVID-19 prevention clinical trial.

Test Product, Dose and Mode of Administration:

The following supplies will be used for vaccination in the study:

- SARS-CoV-2 rS (5 µg) + Matrix-M1 adjuvant (50 µg)

Study vaccination regimens will comprise 2 IM injections (Day 0 and Day 21 + 7 days), preferably in alternating deltoids, with the trial vaccine assigned in a full dose injection volume of 0.5 mL.

Reference Therapy, Dose and Duration of Administration:

Placebo (normal saline, 0.5 mL) will be provided by the Sponsor.

Duration of Treatment:

The duration of the study, excluding screening, is approximately 24 months for each participant.

Statistical Methods and Sample Size Calculation:

The sample size is driven by the total number of cases expected to achieve statistical significance for the primary efficacy endpoint; a total of up to approximately 30,000 participants ≥ 18 years of age will be enrolled to provide a target of 144 symptomatic COVID-19 illness PCR-confirmed SARS-CoV-2 infections.

Two formal interim analyses of efficacy and futility will be conducted based on the accumulation of approximately 50% and 75% of the total anticipated primary endpoints using O'Brien-Fleming boundary conditions.

The following analysis sets are identified for analysis:

Intent-to-Treat Efficacy (ITT) Analysis Set

The ITT analysis set will include all participants who are randomized, regardless of protocol violations or missing data. The ITT analysis set will be used for participant disposition summaries and will be analyzed according to the treatment arm in which the participant was randomized.

Full Analysis Set (FAS)

The FAS will include all participants who are randomized and received at least 1 dose of study vaccine/placebo, regardless of protocol violations or missing data. The FAS population will be analyzed according to the treatment group to which they were randomized. The FAS analysis sets will be used for supportive analyses.

Safety Analysis Set

The safety analysis set will include all participants who receive at least 1 dose of trial vaccine. Participants in the safety analysis set will be analyzed according to the vaccine actually received. In cases where information is available that indicates that a participant received both active and placebo, the participant will be analyzed as part of the active group.

Per-Protocol Efficacy (PP-EFF) and Immunogenicity (PP-IMM) Analysis Sets

The PP-EFF analysis set will include all participants who receive the full prescribed regimen of trial vaccine and have no major protocol deviations that occur before the first COVID-19 positive episode and are determined to affect the efficacy outcomes, including baseline SARS-CoV-2 seropositivity. Although the study will enroll participants regardless of SARS-CoV-2 serologic status at the time of vaccination, any participants with confirmed infection or prior infection due to SARS-CoV-2 at baseline, by nasal swab PCR or serology, will be excluded from the PP-EFF population. PP-EFF will be the primary set for all efficacy endpoints.

The PP-IMM analysis set will be determined for each study visit. The PP-IMM analysis set will include participants that have at least a baseline and 1 serum sample result available after vaccination and have no major protocol violations that are considered clinically relevant to impact immune response at the corresponding study visit, including nasal PCR-positive swabs or seropositivity for SARS-CoV-2 prior to the visit in question. For participant visits on or after Day 21, participants must receive the second vaccination to be included in the PP-IMM analysis set. Prior exposed participants will be determined using baseline SARS-CoV-2 nasal swab or seropositivity at screening to assess if immune responses differ between previously exposed and unexposed individuals.

The review and determination for exclusion from the PP analysis set will be carried out in a blinded fashion by a study clinician prior to unblinding for the interim analysis based on all available information from the locked database.

Primary Endpoint

The primary endpoint will be analyzed on the PP-EFF analysis set and supported by analysis of the FAS.

The VE is defined as VE (%) = (1 – RR) x 100, where RR = relative risk of incidence rates between the 2 trial vaccine groups (SARS-CoV-2 rS / Placebo). The RR will be estimated by exponentiating the treatment group coefficient from a Poisson regression analysis with robust error variance [Zou 2004]. The age strata will be included in the model as a covariate. To assess incidence rates rather than absolute counts of cases, accounting for differences in follow-up times starting with 7 days after the second vaccination among participants, an offset will be utilized in the Poisson regression. A two-sided, alpha level adjusted confidence interval (CI) will be constructed around the estimate.

A super superiority of the VE at each analysis will be used to determine success of the primary endpoint. An alpha level adjusted hypothesis test will be constructed with the following hypotheses:

H_0: VE ≤ 0.30 (RR ≥ 0.70)

H_1: VE > 0.30 (RR < 0.70)

Rejection of the null hypothesis demonstrates a statistically significant VE with a lower bound of CI > 30%. In order to be considered for emergency use authorization or licensure by the United States Food and Drug Administration (FDA), a vaccine must show super superiority where there is a minimum VE of 50% and a lower bound of two-sided alpha adjusted confidence bound of at least 30%. Based upon the number of primary efficacy endpoints planned for analysis, a lower bound of more than 30% corresponds with a VE point estimate of at least 50%.

Secondary Endpoints

The key secondary efficacy endpoint and other secondary efficacy endpoints will be analyzed using the same manner as the primary efficacy analysis. The analysis of the key secondary endpoint will be carried out using a one-sided alpha of 0.025 only after the successful demonstration the primary endpoint to preserve the Type I error rate. All remaining secondary efficacy endpoints will also be performed using an unadjusted one-sided 0.025 alpha level.

The secondary immunogenicity analyses will be performed using the PP-IMM analysis set and the FAS.

For the serum antibody levels specific for the SARS-CoV-2 S protein antigen(s) (IgG antibody to SARS-CoV-2 S protein and hACE2 inhibition) and MN, the geometric mean at each study visit, the geometric mean fold rise (GMFR) comparing to the baseline (Day 0) at each post-vaccination study visit, and the GMFR comparing pre- and post-second dose, along with 95% CI will be summarized by trial vaccine group. The 95% CI will be calculated based on the t distribution of the log-transformed values for geometric means or GMFR, then back transformed to the original scale for presentation.

Safety Analyses

Accumulating safety data, blinded to treatment group, will be reviewed weekly by the PSRT to detect possible signals of a concerning frequency or severity of solicited or unsolicited AEs that may require escalation to the DSMB for unblinded review.

In formal analyses, numbers and percentages (with 95% CIs based on the Clopper-Pearson method) of participants with solicited local and systemic AEs through 7 days after each vaccination will be summarized by trial vaccine group and the maximum toxicity grade over 7 days after each vaccination. The duration of solicited local and systemic AEs after each vaccination will also be summarized by trial vaccine group.

Unsolicited AEs will be coded by preferred term and system organ class using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by trial vaccine group as well as by severity and relationship to trial vaccine. All AEs through 28 days after second vaccination; all MAAEs related to vaccine, SAE, or AESI through EoS will be listed separately and summarized by trial vaccine group.

Vital sign measurements will be summarized by trial vaccine group at each time point using descriptive statistics.

Concomitant medications will be summarized by trial vaccine group and preferred drug name as coded using the World Health Organization (WHO) drug dictionary.

Interim Analyses

Two formal interim analyses of efficacy and futility for review by the independent DSMB, as described in the DSMB Charter, will be conducted based on the accumulation of approximately 50% and 75% of the total anticipated primary endpoints. For these analyses, database freeze for analysis of the primary efficacy and selected secondary endpoints (eg, disease severity, key safety and Day 35 immunogenicity endpoints) will be performed to monitor the benefit-risk profile of vaccination in the 2 age strata. The interim analyses will be performed by an unblinded Biostatistics and Programming team and reviewed by the independent DSMB that will make recommendations with regard to the continuation of the trial. Any early stopping for efficacy will be based on the PP-EFF analysis set only. Regardless of the outcomes at either interim analysis or the final analysis, the study will remain blinded at the participant level for study site personnel and study participants until the end of the study (24 months after the first vaccination) while the Sponsor will be unblinded at the participant level to prepare for regulatory submissions. There will be an unblinded biostatistician and programmer isolated (by firewall) from study personnel. They will complete these analyses independent of study team and Sponsor. A separate Statistical Monitoring Plan will include a detailed description of the responsibilities of the ICON unblinded statistician and the communication plan with the DSMB.

The interim analyses will follow standard group-sequential design using the O'Brien-Fleming boundary conditions. The nominal alpha to be spent for the final analysis will be recalculated using the Lan-DeMets alpha spending function based on the actual numbers of events used for the interim analyses and the numbers of endpoints to be used for the final analysis.

In addition, a futility analysis will be performed using the same data set (PP-EFF). The futility analysis will be based on the two-sided 95% CIs for the primary and key secondary efficacy endpoints based on the PP-EFF analysis set. The futility assessment will be carried out for the 2 endpoints based on the upper bound of two-sided 95% CIs (UBCI) without a multiplicity adjustment:

1. UBCI for the primary efficacy endpoint (symptomatic COVID-19) < 50%

2. UBCI for the key secondary efficacy endpoint (moderate/severe COVID-19) < 50%

If both futility criteria are met, the independent DSMB will make recommendations with regard to the discontinuation of the trial, with regard to continued vaccinations and/or blinded follow up of trial participants.

Monitoring Potential Vaccine Harm

The DSMB will monitor the study for potential vaccine harm based on imbalance in the primary efficacy endpoint, ie, all mild, moderate or severe COVID-19 cases, and severe COVID-19 cases between SARS-CoV-2 rS with Matrix-M1 adjuvant versus placebo. For harm monitoring, cases will be counted starting on Day 0 after the first dose of study vaccination. For mild, moderate or severe COVID-19, only cases where the onset of symptoms is on Day 4 or later will be included. If the prespecified stopping boundary is reached for either mild, moderate and severe COVID-19 or severe COVID-19, then the ICON unblinded statistician will immediately inform the DSMB that the harm rules have been met. This monitoring guideline is chosen to allow stopping for prudence as early as possible, maximizing participant safety.

Data and Safety Monitoring Board

A centralized DSMB will be established in collaboration with NIH, NIAID, Biomedical Advanced Research and Development Authority (BARDA) and Novavax according to the charter dictated by the participating groups. This group will then review interim unblinded data on a monthly basis and make recommendations with respect to safety and emerging efficacy. Furthermore, the DSMB may recommend that the trial be terminated or that specific groups be withdrawn from the study, if any subgroup manifests serious or widespread side effects. The DSMB will be informed immediately by the ICON unblinded statistician if the pre-specified stopping boundary is met, indicating that the vaccine causes harm by increasing the rate of mild, moderate or severe COVID-19. In addition, the DSMB will monitor the study for high vaccine efficacy or for futility to detect vaccine activity.

Date of the Protocol: 16 November 2020

3 SCHEDULE OF ASSESSMENTS

The Schedule of Assessments (SoA) is presented in Table 1.

Table 1 Schedule of Assessments

Study Period:	Screening Period	Primary Vaccination Period				Unscheduled Visits			Months Following Last Vaccination			
						Acute Illness[3]	Convalescent[4]	General[5]				
Study Day:	**–30 to 0**	**0[1]**	**21**	**35**	**Month 3**	–	–	–	**6**	**12[23]**	**18[23]**	**24[23]**
Window (days)[2]:	–	**0**	**+ 7**	**+ 7**	**+ 15**	–	–	–	**± 15**	**± 15**	**± 30**	**± 30**
Minimum Days Following Most Recent Vaccination[2]:	–	**0**	**21**	**14**	**84**	–	–	–	**180**	**360**	**540**	**720**
Days Following Most Recent Vaccination[2]	–	–	–	–	–	–	–	–	**180**	**360**	**540**	**720**
Study Visit:	**Screening**	**1**	**2**	**3**	**4**	**Acute Illness**	**Convalescent**	**General**	**5**	**6**	**7**	**EoS[6]**
Informed consent	X											
Medical and social history[7]	X											
Inclusion/exclusion criteria	X	X[8,9]	X[8,9]									
Demographics[10]	X											
Prior/concomitant medications		X[8,9]	X[8,9]	X	X	X	X	X	X[11]	X[11]	X[11]	X[11]
Vital sign measurements (including body temperature)	X	X[12]	X[12]									
Urine pregnancy test[13]	X	X[9]	X[9]									
Targeted physical examination[14]	X	X[9]	X[9]	X	X	X[15]	X	X	X	X		
Blood sampling for SARS-CoV-2 (anti-NP) antibodies		X[9]		X	X	X	X		X	X	X	X
Vaccination		X	X									
Reactogenicity[16,17]		X	X									
Blood sampling for SARS-CoV-2 vaccine immunogenicity (IgG antibody to SARS-CoV-2 S protein, MN, hACE2 inhibition)		X[9]	X[9]	X	X	X	X		X	X	X	X
Blood sampling for whole blood, CMI[18]		X	X	X								
Monitoring for COVID-19 illness[19]		From 4 days after initial vaccination using eDiary										
Nasal swab(s) at clinic – anterior nares[3]		X[9]				X						

Study Period:	Screening Period	Primary Vaccination Period				Unscheduled Visits			Months Following Last Vaccination			
						Acute Illness[3]	Convalescent[4]	General[5]				
Study Day:	**–30 to 0**	**0[1]**	**21**	**35**	**Month 3**	–	–	–	**6**	**12[23]**	**18[23]**	**24[23]**
Window (days)[2]:	–	**0**	**+ 7**	**+ 7**	**+ 15**	–	–	–	**± 15**	**± 15**	**± 30**	**± 30**
Minimum Days Following Most Recent Vaccination[2]:	–	**0**	**21**	**14**	**84**	–	–	–	**180**	**360**	**540**	**720**
Days Following Most Recent Vaccination[2]	–	–	–	–	–	–	–	–	**180**	**360**	**540**	**720**
Study Visit:	**Screening**	**1**	**2**	**3**	**4**	**Acute Illness**	**Convalescent**	**General**	**5**	**6**	**7**	**EoS[6]**
Nasal self-swab(s) by participant – anterior nares[19]		Starting on Day 4, when fever or other specified symptoms are reported in the eDiary for at least 2 consecutive days for the same symptom, participants will begin daily nasal self-swabbing within 3 days of symptom onset at home for a total of 3 days to ensure capture of intermittent shedding										
Daily oxygen saturation via pulse oximeter (supplied by study site at Unscheduled Acute Illness Visit)[3]			At Unscheduled Acute Illness Visit, study site records O_2 saturation measured while training the participant on the use of the device and provides the device for use at home until symptoms resolve									
All unsolicited AEs since prior visit		X	X	X	X[20]	X[20]	X[20]					
All MAAEs		X	X	X	X[20]	X[20]	X[20]					
MAAEs since last visit						X[20]	X[20]					
Any MAAE attributed to vaccine		X	X	X	X	X	X	X	X	X	X	X
SAEs	X	X	X	X	X	X	X	X	X	X	X	X
AESI[21]	X	X	X	X	X	X	X	X	X	X	X	X
Endpoint Review[4]							X					
EoS form[22]												X

Abbreviations: AE = adverse event; AESI = adverse event(s) of special interest; BMI = body mass index; BP = blood pressure; CMI = cell-mediated immunity; COVID-19 = coronavirus disease 2019; eDiary = electronic patient-reported outcome diary application; ELISA = enzyme-linked immunosorbent assay; EoS = end of study; FDA = United States Food and Drug Administration; FLU-PRO = InFLUenza Patient-Reported Outcome; hACE2 = human angiotensin-converting enzyme 2; HIV = human immunodeficiency virus; MAAE = medically attended adverse event; MN = microneutralization; NP = nucleoprotein; O_2 = oxygen; PBMC = peripheral blood mononuclear cells; PIMMC = potential immune-mediated medical conditions; PCR = polymerase chain reaction; RNA = ribonucleic acid; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; Th1 = type 1 T helper; Th2 = type 2 T helper.

1. If screening and randomization occur on the same day (ie, Day 0), study visit procedures should not be duplicated.
2. Days relative to vaccination are only estimates because the window allowance is not inclusive. Should a study pause occur, visits/windows will be adjusted to allow participants to continue without protocol deviation. Visit schedules following the vaccinations are calculated relative to the day the vaccinations were received.
3. At the in-person Unscheduled Acute Illness Visit, participants will be queried regarding AE symptoms, concomitant medications taken for these symptoms, undergo a targeted physical examination (to include O_2 saturation), if indicated, and have obtained by the study personnel a medically attended nasal swab, a blood sample for serologic testing and be trained on the use of the portable pulse oximeter that they will take home with them.

Study Period:	Screening Period	Primary Vaccination Period				Unscheduled Visits			Months Following Last Vaccination			
						Acute Illness[3]	Convalescent[4]	General[5]				
Study Day:	–30 to 0	0[1]	21	35	Month 3	–	–	–	6	12[23]	18[23]	24[23]
Window (days)[2]:	–	0	+ 7	+ 7	+ 15	–	–	–	± 15	± 15	± 30	± 30
Minimum Days Following Most Recent Vaccination[2]:	–	0	21	14	84	–	–	–	180	360	540	720
Days Following Most Recent Vaccination[2]	–	–	–	–	–	–	–	–	180	360	540	720
Study Visit:	Screening	1	2	3	4	Acute Illness	Convalescent	General	5	6	7	EoS[6]

4. Study participants whose home nasal self-swab and/or medically attended nasal swabs are confirmed to be PCR-positive for SARS-CoV-2 at the Unscheduled Acute Illness Visit will be contacted by the study site to arrange an Unscheduled Convalescent Visit. The Unscheduled Convalescent Visit will occur approximately 1 month (or as soon thereafter, as feasible) after the onset of the PCR-confirmed case of COVID-19 at the Unscheduled Acute Illness Visit to assess status of AEs, record the clinical course of the disease on the Endpoint Form and obtain a blood sample for convalescent serologic testing. Pulse oximeters should be returned to the study site at this visit.
5. An Unscheduled General Visit will be conducted by study personnel in the event of a general medical issue other than COVID-19 symptomatology.
6. EoS visit. Should participants decide to terminate early, an EoS telephone visit will occur to collect the maximum safety data and blood sample, if possible.
7. Including prior and concomitant medical conditions, recent vaccinations (≤ 90 days), and significant surgical procedures.
8. Should participants start specific medications or have specific diagnoses that were exclusionary at baseline, consultation with the ICON Medical Monitor or Sponsor is required.
9. Performed prior to vaccination.
10. Screening only. Including date of birth (day, month, and year), sex, race, ethnicity, weight, height, and BMI (derived).
11. Only those medications associated with any MAAE attributed to vaccine, potential AESI, or SAE will be recorded. For day of second dose, recording is prior to vaccination.
12. On vaccination days, vital sign measurements will be collected once before vaccination to ensure participant has controlled BP and heart rate and no evidence of fever prior to vaccination.
13. For participants of childbearing potential, a urine pregnancy test will be performed at screening and prior to each vaccination. A positive urine pregnancy test at either time will result in the participant not receiving any further vaccination.
14. Examination at screening to include height and weight. Targeted physical examination after Day 21 is optional, as needed for AE evaluation.
15. Targeted physical examination at Unscheduled Acute Illness Visit should include recording of O_2 saturation measured during the process of training the study participant in the use of the device.
16. On vaccination days, participants will remain in clinic for at least 30 minutes to be monitored for any severe reactogenicity. Severe reactions will be noted as AEs on day of vaccination. Following receipt of vaccine, reactogenicity events that occur after completion of 4 days of reactogenicity reporting (via eDiary) and that meet the criteria for nasal swab for COVID-19 (eg, fever, generalized myalgia, etc) should prompt notification of the study site, collection of a nasal swab and follow-up according to the directions for COVID-19 surveillance.
17. Participants will utilize an eDiary to record reactogenicity following vaccination. All participants will record reactogenicity starting on the same day of the

Study Period:	Screening Period	Primary Vaccination Period				Unscheduled Visits			Months Following Last Vaccination			
						Acute Illness[3]	Convalescent[4]	General[5]				
Study Day:	–30 to 0	0[1]	21	35	Month 3	–	–	–	6	12[23]	18[23]	24[23]
Window (days)[2]:	–	0	+ 7	+ 7	+ 15	–	–	–	± 15	± 15	± 30	± 30
Minimum Days Following Most Recent Vaccination[2]:	–	0	21	14	84	–	–	–	180	360	540	720
Days Following Most Recent Vaccination[2]	–	–	–	–	–	–	–	–	180	360	540	720
Study Visit:	Screening	1	2	3	4	Acute Illness	Convalescent	General	5	6	7	EoS[6]

vaccinations and for an additional 6 days (not counting vaccination day). Study site personnel will regularly review the eDiary for completeness. Should any reactogenicity event extend beyond 7 days after vaccination (toxicity grade ≥ 1), then it will be recorded as an AE with the same start date as the reactogenicity event and followed to resolution per FDA guidelines for dataset capture.

18. Subset of participants (< 100) enrolled at pre-identified study site(s) with the capability to process blood samples for PBMC.
19. Participants will be provided with a thermometer and instructed to monitor their body temperature daily throughout the study and to record temperature and relevant symptoms daily in their eDiary. Participants who are noted during regular monitoring of the daily eDiary entries to not have reported temperature and symptoms for ≥ 7 days will be contacted by phone to assess clinical situation and maintain engagement in the study. Starting on Day 4, throughout the first 12 months of the study, when fever or other specified symptoms (see Table 3 for symptoms suggestive of COVID-19) are reported in the eDiary for at least 2 consecutive days for the same symptom, participants will be directed via the eDiary to begin daily nasal self-swabbing for PCR testing within 3 days of symptom onset at home for a total of 3 consecutive days and to initiate daily completion of the FLU-PRO symptom reporting instrument for 10 days after COVID-19 symptom onset or until the participant experiences 2 consecutive asymptomatic days. In addition, the eDiary will alert the study site to contact the participant to schedule the in-person Unscheduled Acute Illness Visit.
20. Through Day 49.
21. AESI: To include PIMMC (listed in Appendix 2, Table 7), or any newly identified potential AESI followed through 24 months after participants' final vaccination. Complications of COVID-19 (listed in Appendix 2, Table 8) should be considered and reported as AESIs.
22. EoS form will be completed for all participants, including those who are terminated early.
23. From Months 12 to 24, study sites will initiate monthly remote contacts (phone, email, text) with participants to collect SAEs, MAAEs attributed to vaccine, AESIs or COVID-19 illness.

4 TABLE OF CONTENTS

4.1 List of Tables

4.2 List of Figures

4.3 List of Appendices

5 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

24/7	24 hours 7 days a week
AE	Adverse event
AESI	Adverse event of special interest
ALCOAC	Attributable, legible, contemporaneous, original, accurate, and complete
AMI	Acute myocardial infarction
ANCA	Anti-neutrophil cytoplasmic antibody
ARDS	Acute respiratory distress syndrome
BARDA	Biomedical Advanced Research and Development Authority
BiPAP	Bilevel positive airway pressure
BMI	Body mass index
BP	Blood pressure
CI	Confidence interval
CMI	Cell-mediated immunity
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease 2019
COVPN	COVID-19 Prevention Network
CPAP	Continuous positive airway pressure
CT	Computerized tomography
DAIDS	Division of AIDS, NIAID, NIH
DBP	Diastolic blood pressure
DSMB	Data and Safety Monitoring Board
DVT	Deep vein thrombosis
EBOV	Zaire ebolavirus
ECMO	Extracorporeal membrane oxygenation
eCRF	Electronic case report form
EDC	Electronic data capture
eDiary	Electronic patient-reported outcome diary application
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EnvD	Envelope dimers
EoS	End of study
ER	Emergency room
EU	European Union

EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS-EFF	Full Analysis Set - Efficacy
FAS-IMM	Full Analysis Set - Immunogenicity
FDA	United States Food and Drug Administration
FLU-PRO	InFLUenza Patient-Reported Outcome (questionnaire)
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMFR	Geometric mean fold rise
GMT	Geometric mean titer
GP	Glycoprotein
HA	Hemagglutinin
hACE2	Human angiotensin-converting enzyme 2
HIV	Human immunodeficiency virus
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
ICU	Intensive care unit
IEC	Independent Ethics Committee
IFN-γ	Interferon gamma
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IL	Interleukin
IM	Intramuscular
IND	Investigational New Drug
IRB	Institutional Review Board
ITT-EFF	Intent-to-Treat Efficacy
ITT-IMM	Intent-to-Treat Immunogenicity
IV	Intravenous
IWRS	Interactive web response system
LRTI	Lower respiratory tract infection
MAAE	Medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East Respiratory Syndrome
MN	Microneutralization
NHP	Nonhuman primate

NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NIPPV	Non-invasive positive pressure ventilation
NIV	Non-invasive ventilation
NP	Nucleocapsid
NZW	New Zealand White
O_2	Oxygen
OWS	Operation Warp Speed
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
PE	Pulmonary embolism
PHEIC	Public health emergency of international concern
PIMMC	Potential immune-mediated medical conditions
PP-EFF	Per-protocol efficacy
PP-IMM	Per-protocol immunogenicity
PSRT	Protocol Safety Review Team
PVSS	Pharmacovigilance and Safety Services
r	Recombinant
RNA	Ribonucleic acid
RR	Relative risk
RSV	Respiratory syncytial virus
S	Spike
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV	Severe acute respiratory syndrome coronavirus
SBP	Systolic blood pressure
SoA	Schedule of assessments
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
Th1	Type 1 T helper
Th2	Type 2 T helper
TNF-α	Tumor necrosis factor alpha
US	United States
VE	Vaccine efficacy

VLP	Virus-like particle
WHO	World Health Organization
ZIKV	Zika virus

6 INTRODUCTION

6.1 Background

Coronaviruses are medium sized, enveloped, positive-stranded ribonucleic acid (RNA) viruses, with a characteristic crown-like appearance in electron micrographs due to circumferential studding of the viral envelope with projections comprising the S protein. There are 4 different strains (229E, OC43, NL63, and HKU1), which are ubiquitous in humans and generally result in mild upper respiratory illnesses and other common cold symptoms including malaise, headache, nasal discharge, sore throat, fever, and cough [Su 2016]. In addition, other coronavirus strains are widespread in animals, where they typically cause enteric disease. These zoonotic coronaviruses have been known to evolve into strains that can infect humans with serious consequences including severe acute respiratory syndrome coronavirus (SARS-CoV) from 2002 to 2003, Middle East Respiratory Syndrome (MERS)-CoV since 2012, and most recently, the novel SARS-CoV-2 since 2019 [Habibzadeh 2020].

In late December of 2019, an outbreak of respiratory disease caused by novel coronavirus (2019-nCoV) was detected in Wuhan, Hubei province, China. The virus' rapidly discerned genetic relationship with the 2002-2003 SARS-CoV has resulted in adoption of the name "SARS-CoV-2," with the disease being referred to as coronavirus disease 2019 (COVID-19). Despite containment efforts since the start of the outbreak, the SARS-CoV-2 has spread rapidly with over 214 countries/territories/areas outside of China reporting laboratory confirmed COVID-19 cases as of 15 May 2020 [WHO 2020] On 30 January 2020, the International Health Regulations Emergency Committee of the World Health Organization (WHO) designated the outbreak as a public health emergency of international concern (PHEIC) and subsequently declared a pandemic on 11 March 2020.

Novavax, Inc. is developing a recombinant vaccine adjuvanted with the saponin-based Matrix-M1™ adjuvant for the prevention of disease caused by SARS-CoV-2. SARS-CoV-2 recombinant (r) spike (S) protein nanoparticle vaccine (SARS-CoV-2 rS) is constructed from the full-length, wild-type SARS-CoV-2 S glycoprotein (GP) based on the GenBank gene sequence MN908947, nucleotides 21563-25384 from the 2019 SARS-CoV-2 genome. The S protein is a type 1 trimeric glycoprotein of 1,273 amino acids that is produced as an inactive S0 precursor. The S-gene was codon-optimized for expression in *Spodoptera frugiperda* insect cells. The SARS-CoV-2 rS nanoparticle vaccine is intended for administration with Matrix-M1 adjuvant, which is a saponin-based adjuvant that has previously been shown to enhance the immunogenicity of other nanoparticle vaccines in nonclinical and clinical studies.

The purpose of this study is to evaluate the efficacy, safety, and immunogenicity of SARS-CoV-2 rS with Matrix-M1 adjuvant in adult participants ≥ 18 years of age. Clinical endpoints will be assessed overall, and also within age subgroups, with the main age strata 18 to

64 years and ≥ 65 years. All study participants will receive 2 doses of trial vaccine, on Days 0 and 21 + 7 days. The dose/immunization schedule implemented in this study is based on the optimal safety and immunogenicity data observed in the nonclinical and early clinical studies.

6.2 Nonclinical Summary

In support of the development of SARS-CoV-2 rS, Novavax has obtained nonclinical pharmacology data concerning several SARS-CoV-2 S protein variants, toxicity data concerning SARS-CoV-2 rS with Matrix-M1 adjuvant, and prior toxicity data concerning other viral glycoproteins manufactured in the baculovirus-Sf9 system and formulated with Matrix-M1 adjuvant.

Nonclinical Data from SARS-CoV-2 Spike Protein Constructs that Support SARS-CoV-2 rS Development

Mouse immunogenicity studies were conducted to evaluate several SARS-CoV-2 S protein variants and select the vaccine candidate [Tian 2020]. The selected vaccine candidate, BV2373 (3Q-2P), was demonstrated to be immunogenic and elicited functional antibodies. For the tested constructs, shallow dose responses with Matrix-M1 adjuvant were observed, suggesting that the adjuvant may be significantly antigen-sparing in large animals and humans.

The candidate SARS-CoV-2 rS vaccine, based on the BV2373 construct, has been evaluated in dose titration studies in [redacted] cynomolgus macaques and baboons. [redacted] In cynomolgus macaques, 2-dose regimens of 5 or 25 µg SARS-CoV-2 rS/25 or 50 µg Matrix-Ml adjuvant were also highly immunogenic, resulting in high anti-S IgG levels, high hACE2 binding inhibition titers, and high neutralizing antibody responses. The 5 and 25 µg antigen doses gave generally similar responses when administered twice with 50 µg of Matrix-Ml adjuvant. In baboons, which may be more predictive of responses in humans, 5 and 25 µg SARS-CoV-2 rS/50 µg Matrix-Ml adjuvant induced high levels of anti-S IgG, hACE2-binding inhibiting antibodies, and neutralizing antibodies. Matrix-Ml adjuvant provided antigen-sparing, and supported induction of functional antibodies. Importantly, Matrix-Ml adjuvanted SARS-CoV-2 rS also appeared to induce strong Thl type CD4+ T cell responses to SARS-CoV-2 spike protein which included polyfunctional effector phenotypes. Current data in this small baboon study confirms that doses of 5 µg and 25 µg with 50 µg Matrix-M1 were the correct doses to test clinically, with Matrix-M1 adjuvant appearing critical for maximum responses. This finding was confirmed in a Phase 1 trial in humans [Keech 2020].

Virus challenge studies were performed in mice, [redacted] and cynomolgus macaques. In 2 mouse challenge models, immunization with 1 or 2 doses of SARS-CoV-2 rS/Matrix-M1

adjuvant suppressed viral replication, reduced lung inflammation, and reduced systemic morbidity (weight loss) after SARS-CoV-2 live virus challenge and were not associated with any obvious exacerbation of the inflammatory response to the virus or worsening of clinical outcomes. The best responses were seen in animals receiving 2 doses of adjuvanted vaccine.

[redacted]

Cynomolgus macaques, administered with human doses of 5 or 25 µg SARS-CoV-2 rS adjuvanted with 50 µg Matrix-M1 had high and comparable levels of anti-S IgG titers and hACE2 receptor binding inhibition titers detected 21 days after the first immunization. All of the macaques immunized with any dose or regimen of SARS-CoV-2 rS/Matrix-M1 adjuvant were protected against live virus challenge as evidenced by the reduction of total viral RNA and subgenomic RNA to below the limit of quantitation in bronchoalveolar lavages and nasal swabs.

[redacted]

Nonclinical Data from Other Baculovirus-Sf9-Produced Nanoparticle Vaccines that Support SARS-CoV-2 rS Development

The immunogenicity and protective efficacy of 2002-2003 SARS-CoV S protein and chimeric influenza/SARS-CoV virus-like particle (VLP) vaccines produced in the baculovirus-Sf9 system and administered with and without aluminum hydroxide adjuvants was demonstrated in a mouse challenge study [Liu 2011]. Robust neutralizing antibody titers were observed following vaccination, although both antigens required adsorption to aluminum hydroxide for optimal responses. The immunogenicity and protective efficacy of a MERS-CoV S nanoparticle vaccine with and without Matrix-M1 adjuvant was demonstrated in a mouse challenge study [Coleman 2017]. Following vaccination, the MERS-CoV S nanoparticle was immunogenic across all active treatment groups; however, the presence of Matrix-M adjuvant induced a 3 to > 10-fold enhancement of the binding and neutralizing antibody responses. In addition, Matrix-M1 adjuvant essentially eliminated the antigen dose-response, suggesting the potential for major antigen-sparing and consequent improved manufacturing efficiency and timeliness [Coleman 2017]. The Matrix-M1 adjuvant was also shown to enhance antibody, cellular, and protective immune responses in Balb/c mice administered Zaire ebolavirus (EBOV) GP vaccine with or without Matrix-M1 or aluminum phosphate adjuvants [Bengtsson 2016].

In addition, 3 GLP-compliant toxicology studies in NZW rabbits have been performed with 4 different antigens (influenza hemagglutinin [HA] ± respiratory syncytial virus [RSV] F, Zika virus envelope dimers [ZIKV EnvD], and EBOV GP), in which up to 100 µg Matrix-M1 adjuvant alone or with antigen was evaluated. These toxicological investigations indicated that baculovirus-Sf9-produced antigens (up to 240 µg total nanoparticle dose) with Matrix-M1 adjuvant (up to 100 µg) were well tolerated in the animals tested with no evidence of toxicity suggestive of any unusual risk or target organ for toxicity. Non-adverse findings, including local injection site inflammation, enlargement of the lymph nodes draining the injection sites, and elevated serum markers of inflammation (including C-reactive protein), were transient and were considered consistent with immune system stimulation consequent to immunization.

Further details are provided in the SARS-CoV-2 rS Investigator's Brochure (IB).

6.3 Clinical Summary

The first clinical study with SARS-CoV-2 rS nanoparticle vaccine is 2019nCoV-101, which is a 2-part, randomized, observer-blinded, placebo-controlled, Phase 1/2 trial. Part 1 (Phase 1) is designed to evaluate the immunogenicity and safety of SARS-CoV-2 rS nanoparticle vaccine with or without Matrix-M1 adjuvant in 131 healthy participants ≥ 18 to ≤ 59 years of age. Results of an interim analysis for the Phase 1 portion of the trial at Day 35 showed that SARS-CoV-2 rS with Matrix-M1 adjuvant was well tolerated and elicited robust immune responses. There were no serious adverse events (SAEs) or adverse events of special interest (AESIs) reported. Reactogenicity was mainly mild in severity and of short duration (mean ≤ 2 days), with second vaccinations inducing greater local and systemic reactogenicity. The adjuvant significantly enhanced immune responses (anti-S IgG, hACE2 receptor binding inhibition antibody, and neutralizing antibody) and was antigen dose-sparing; the 2-dose 5 µg SARS-CoV-2 rS/Matrix-M1 adjuvant induced mean anti-S IgG and neutralizing antibody responses that exceeded the mean responses in convalescent sera from COVID-19 patients with clinically significant illnesses. The vaccine also induced antigen-specific T cells with a largely Type 1 T helper (Th1) phenotype.

Part 2 (Phase 2) is designed to evaluate the immunogenicity, safety and preliminary efficacy of SARS-CoV-2 rS and Matrix-M1 adjuvant in up to 1,500 healthy adults ≥ 18 to ≤ 84 years of age with more co-morbidities than the participant population in Part 1 of the study. An interim 5-day reactogenicity analysis was conducted on 846 participants following the first dose of study vaccine to support initiation of the Phase 3 study. This analysis comprised 607 participants aged 18 to 59 years (the same age range of Part 1 of the study) and 239 participants aged 60 to 84 years, with data presented in masked groups to maintain the integrity of the study. Overall, local and systemic reactogenicity data from this analysis were consistent with the reactogenicity data in Part 1 of the study, with no safety concerns between the younger and older age cohorts. Both local and systemic reactogenicity events occurred less frequently in older adults.

Novavax has, in its internally-sponsored clinical trials, tested baculovirus-Sf9-produced nanoparticle vaccines in 14,848 participants comprising older adults, young adults, and a limited number of children 2 to 5 years of age; and also including 3,075 pregnant women, with acceptable safety. Matrix-M1 adjuvant has been given to 4,311 humans (of which, approximately 2,657 humans received nanoparticle vaccine) with acceptable short-term reactogenicity and an unremarkable long-term safety profile.

Further details are provided in the SARS-CoV-2 rS IB.

6.4 Study Rationale

Both nonclinical and early clinical data to date support continued clinical development of SARS-CoV-2 rS and Matrix-M1 adjuvant as a potential vaccine against SARS-CoV-2. In rodent and nonhuman primate (NHP) challenge models, Matrix-M1 adjuvanted SARS-CoV-2 rS induced high titers of antibodies in a dose-dependent fashion, as measured against anti-spike protein and hACE2 receptor binding, achieved neutralization of wild-type virus that exceeded the magnitude of responses measured in human convalescent sera and provided protection against SARS-CoV-2 challenge [Tian 2020; Mandolesi 2020; Guebre-Xabier 2020]. Notably, in NHP studies, clinical doses of vaccine (5 and 25 µg SARS-CoV-2 rS/50-µg Matrix-M1) resulted in sterile immunity in the lungs and nasal passage following wild-type virus challenge, suggesting that the vaccine may both protect against upper and lower respiratory tract disease and interrupt transmission [Guebre-Xabier 2020].

Results from a Day 35 interim analysis of Part 1 (Phase 1) of Study 2019nCoV-101 indicate that in 131 healthy adult participants 18 to 59 years of age, 2-dose regimens of 5 and 25 µg SARS-CoV-2 rS/50 µg Matrix-M1 (on Days 0 and 21) were well tolerated and induced robust immune responses with high levels of neutralizing antibodies that closely correlated with anti-spike IgG [Keech 2020]. IgG and neutralizing antibody responses following the second dose of vaccine were very high, generally exceeded the titers seen in convalescent serum from hospitalized COVID-19 patients and exceeded overall convalescent sera geometric mean titers (GMTs) by 4-fold. The benefit of Matrix-M1 adjuvant was clear in the greater magnitude of humoral and T-cell response, induction of functional antibodies, and dose-sparing.

A Phase 2 clinical program is underway and will provide additional safety and immunogenicity results in older participants (> 60 years of age) and participants with co-morbidities. Reactogenicity data following the first dose indicate that the reactogenicity profile between adults 18 to 59 years and older adults ≥ 60 years are comparable, with older adults generally reporting solicited events less frequently. Combining the current nonclinical and clinical data with positive Phase 1/2 data provide the impetus for early initiation of the Phase 3 clinical development program in the context of the current public health pandemic crisis.

The purpose of this Phase 3 study is to evaluate the efficacy, safety and immunogenicity of SARS-CoV-2 rS with Matrix-M1 adjuvant in adult participants ≥ 18 years of age. Clinical

endpoints (see Sections 7.4 to 7.6) will be assessed overall, and within age subgroups, with the main age strata 18 to ≤ 64 years and ≥ 65 years. All participants will receive 2 doses of trial vaccine: 1 dose on each of Days 0 and 21 + 7 days. This schedule is based on clinical data from the Phase 1/2 clinical program. If this vaccine or another is demonstrated to be safe and efficacious and approved by regulatory authorities, participants for whom the new vaccine is recommended and available will be counseled with respect to their options. These participants may be offered the opportunity to be unblinded so that those who received placebo may be offered the Novavax vaccine or another product, as appropriate, outside the protocol procedures. Participants who are unblinded and receive an active vaccine in this manner will be censored in the final analysis at the time of unblinding but will be strongly encouraged to remain in safety follow-up as defined in the protocol.

6.5 Rationale for Dose Selection

Clinical doses of vaccine and adjuvant (5 and 25 µg SARS-CoV-2 rS adjuvanted with 50 µg Matrix M1) administered in 2 doses resulted in sterilizing immunity in the lungs and nasal passage following wild-type virus challenge in NHP, suggesting that the vaccine may protect against both upper and lower respiratory tract disease and interrupt transmission [Guebre-Xabier 2020]. These dose levels are being evaluated in Part 1 of Study 2019nCoV-101 in 131 healthy adult participants 18 to 59 years of age and in Part 2 of Study 2019nCoV-101 in 750 to 1,500 participants 18 to 84 years of age, including participants with co-morbidities. Results from the Part 1 Day 35 interim analysis support either dose of SARS-CoV-2 rS/Matrix-M1 adjuvant in terms of safety and immunology, with the lower dose (5 µg) offering the advantage of dose-sparing [Keech 2020]. Based on the available nonclinical and Phase 1 data, the dose selected for the Phase 3 study is 5 µg SARS-CoV-2 rS/50 µg Matrix-M1 adjuvant administered as an intramuscular (IM) injection on Days 0 and 21. All vaccinations will be administered on an outpatient basis by designated study site personnel in a way to maintain the blind. Pharmacy management of unblinded product will be performed by unblinded study site personnel who may administer the study vaccine, if qualified to do so, but will not otherwise be involved in the study procedures or observation of participants.

6.6 Benefit – Risk Assessment

The SARS-CoV-2 rS nanoparticle vaccine contains purified protein antigens. It cannot replicate, the protein is not produced using infectious SARS-CoV-2, nor can the vaccine cause COVID-19. However, in common with all vaccines produced in cell culture or other systems, the SARS-CoV-2 rS nanoparticle vaccine contains residual non-vaccine proteins derived from the production system, and sensitization to these, or the SARS-CoV-2 S protein itself, may theoretically occur. While the occurrence of immediate hypersensitivity is possible with the administration of any vaccine, whether licensed or in development, no such reactions have been observed in any of the Sponsor's clinical trials to date. As clinical data become available with

increased exposure, it is possible that this profile may change. The risk of AEs related to hypersensitivity will be mitigated by observation of participants for at least 30 minutes after each study vaccination.

The risk for enhanced COVID-19 in immunized participants is a theoretical risk. Enhanced disease in coronavirus vaccine-immunized animals after infectious virus challenge has been demonstrated in nonclinical studies of several, but not all, coronavirus vaccine candidates. There is currently no evidence for immunoenhancement in nonclinical testing of SARS-CoV-2 rS or other Novavax baculovirus-Sf9-based vaccines taken into nonclinical evaluation or clinical trials.

No risks have been identified in nonclinical or early clinical testing of SARS-CoV-2 or other coronavirus vaccines (SARS-CoV and MERS-CoV) developed using the baculovirus-Sf9 system to date. In supportive toxicology studies with other viral GP nanoparticle vaccines developed using the baculovirus-Sf9 system with different antigens, findings were generally consistent with an immune response to the vaccine formulations. These toxicological investigations indicated that baculovirus-Sf9-produced antigens (up to 240 µg total nanoparticle dose) with Matrix-M1 adjuvant (up to 100 µg) were well tolerated in the animal and antigen system tested with no evidence of toxicity suggestive of any unusual risk or target organ for toxicity. Non-adverse findings, including local injection site inflammation and serum chemical markers of inflammation (such as C-reactive protein), were transient and considered consistent with immune system stimulation consequent to immunization.

6.6.1 Risk Assessment

Details of risk-based monitoring are provided in the Monitoring Plan.

6.6.2 Overall Benefit – Risk Conclusion

Findings to date suggest that SARS-CoV-2 rS when administered with Matrix-M1 adjuvant demonstrated an acceptable safety profile in adult participants aged 18 to 84 years and a robust immunogenicity profile in healthy adult participants aged 18 to < 59 years. Results of an interim 5-day reactogenicity analysis on 846 participants aged 18 to 84 years in Part 2 of Study 2019nCoV-101 showed a similar reactogenicity profile between younger and older participants, with both local and systemic reactogenicity events occurring less frequently in older adults.

Novavax baculovirus-Sf9-produced nanoparticle vaccines comprising viral glycoproteins, with and without Matrix-M1 or aluminum adjuvants, have been shown to induce robust and protective immune responses in relevant animal models to influenza HAs, RSV F protein, SARS-CoV and MERS-CoV S proteins, rabies GP, and EBOV GP. In addition, the Novavax RSV F protein candidate adsorbed to aluminum phosphate has induced antibodies in pregnant women which, when transferred transplacentally, were associated with reduced rates of RSV lower respiratory tract infections in their infants during the first 90 to 180 days of life. The goal of this program is

to investigate the efficacy, safety and immunogenicity of the SARS-CoV-2 rS vaccine with Matrix-M1 adjuvant in prevention of COVID-19.

Further details are provided in the SARS-CoV-2 rS IB.

7 STUDY OBJECTIVES, ENDPOINTS AND ESTIMANDS

7.1 Primary Objective:

- To evaluate the efficacy of a primary 2-dose regimen of SARS-CoV-2 rS adjuvanted with Matrix-M1 compared to placebo against polymerase chain reaction (PCR)-confirmed symptomatic COVID-19 illness diagnosed ≥ 7 days after completion of the second vaccination in adult participants ≥ 18 years of age.

7.2 Secondary Objectives:

7.2.1 Key Secondary Objective:

- To evaluate the efficacy of a primary 2-dose regimen of SARS-CoV-2 rS adjuvanted with Matrix-M1 compared to placebo against PCR-confirmed moderate-to-severely symptomatic COVID-19 illness diagnosed ≥ 7 days after completion of the second vaccination in adult participants ≥ 18 years of age.

7.2.2 Other Secondary Objectives:

- To assess vaccine efficacy (VE) against ANY symptomatic SARS-CoV-2 infection.
- To assess VE according to race and ethnicity.
- To assess VE in high-risk adults versus non-high-risk adults (high-risk is defined by age ≥ 65 years with or without co-morbidities or age < 65 years **with** co-morbidities [eg, obesity (body mass index [BMI] > 30 kg/m^2), chronic kidney or lung disease, cardiovascular disease and diabetes mellitus type 2) and/or by life circumstance [living or working conditions involving known frequent exposure to SARS-CoV-2 or to densely populated circumstances (eg, nursing homes, factory or meat packing plants, healthcare providers, etc)]).
- To describe the humoral immune response to vaccine in terms of neutralizing antibody to SARS-CoV-2 for all Immunogenicity Population Participants, and for subsets with and without prior SARS-CoV-2 exposure determined by detectable anti-nucleoprotein (NP) antibodies at baseline.
- To assess the immune response to vaccine by IgG antibody to SARS-CoV-2 S protein and hACE2 inhibiting antibodies at Day 35 and Month 3 for all Immunogenicity Population participants, and for subsets with and without prior SARS-CoV-2 exposure determined by detectable anti- NP antibodies at baseline.
- To assess the durability of immune response (IgG antibody to SARS-CoV-2 S protein, hACE2 inhibition, and microneutralization [MN]) at 6, 12, 18 and 24 months after last vaccination for all Immunogenicity Population participants, and for subsets with and without detectable anti-NP antibodies at baseline.

- To describe and compare the safety experience for the vaccine versus placebo in adult participants ≥ 18 years of age based on solicited short-term reactogenicity by toxicity grade for 7 days following each vaccination (Days 0 and 21).
- To assess overall safety through Day 49 (28 days after second vaccination) and to compare vaccine versus placebo for all unsolicited AEs and medically attended adverse events (MAAEs).
- To assess the frequency and severity of MAAEs attributed to vaccine, AESIs, or SAEs through the end of study (EoS) and to compare vaccine versus placebo.
- To assess all-cause mortality in vaccine versus placebo recipients.
- To describe the severity and course of COVID-19 in vaccine versus placebo recipients in terms of healthcare requirements, utilization and medical assessments.
- To assess the proportion of participants (vaccine versus placebo recipients) with SARS-CoV-2 infection determined by anti-SARS-CoV-2 NP antibodies, including specifically asymptomatic infection, across the 2 years of study follow-up.
- To assess the VE against SARS-CoV-2 infection determined by anti-SARS-CoV-2 NP antibodies, regardless of whether the infection was symptomatic.

7.3 Exploratory Objectives:

- To assess cell-mediated response:
  - Th1 or Type 2 T helper (Th2) predominance.
- To contribute to a larger cross-study National Institutes of Health (NIH) effort to define correlates of risk and protection against SARS-CoV-2 infection and disease.
- To assess impact of vaccination on nasal viral load in nasal swabs of participants who develop symptoms of possible COVID-19.
- To describe sequences of the genetic material from SARS-CoV-2 detected in COVID-19 cases to evaluate possible viral mutations that may be associated with breakthrough infections.

7.4 Primary Endpoint:

First episode of PCR-positive nasal swab **and** ≥ 1 of symptomatic mild, moderate, or severe COVID-19, where severity is defined as:

Mild COVID-19 (≥ 1 of the following):

- Fever (defined by subjective or objective measure, regardless of use of anti-pyretic medications)
- New onset cough
- ≥ 2 additional COVID-19 symptoms:
  - New onset or worsening of shortness of breath or difficulty breathing compared to baseline.
  - New onset fatigue.
  - New onset generalized muscle or body aches.
  - New onset headache.
  - New loss of taste or smell.
  - Acute onset of sore throat, congestion or runny nose.
  - New onset nausea, vomiting or diarrhea.

OR Moderate COVID-19 (≥ 1 of the following):

- High fever (≥ 38.4°C) for ≥ 3 days (regardless of use of anti-pyretic medications, need not be contiguous days).
- Any evidence of significant lower respiratory tract infection (LRTI):
  - Shortness of breath (or breathlessness or difficulty breathing) with or without exertion (greater than baseline).
  - Tachypnea: 20 to 29 breaths per minute at rest.
  - SpO_2: 94% to 95% on room air.
  - Abnormal chest X-ray or chest computerized tomography (CT) consistent with pneumonia or LRTI.
- Adventitious sounds on lung auscultation (eg, crackles/rales, wheeze, rhonchi, pleural rub, stridor).

OR Severe COVID-19 (≥ 1 of the following):

- Tachypnea: ≥ 30 breaths per minute at rest.
- Resting heart rate ≥ 125 beats per minute.
- SpO_2: ≤ 93% on room air or PaO_2/FiO_2 < 300 mmHg.

- High flow oxygen (O_2) therapy or non-invasive ventilation (NIV)/non-invasive positive pressure ventilation (NIPPV) (eg, continuous positive airway pressure [CPAP] or bilevel positive airway pressure [BiPAP]).
- Mechanical ventilation or extracorporeal membrane oxygenation (ECMO).
- One or more major organ system dysfunction or failure to be defined by diagnostic testing/clinical syndrome/interventions, including any of the following:
  - Acute respiratory failure, including acute respiratory distress syndrome (ARDS).
  - Acute renal failure.
  - Acute hepatic failure.
  - Acute right or left heart failure.
  - Septic or cardiogenic shock (with shock defined as systolic blood pressure [SBP] < 90 mm Hg OR diastolic blood pressure [DBP] < 60 mm Hg).
  - Acute stroke (ischemic or hemorrhagic).
  - Acute thrombotic event: acute myocardial infarction (AMI), deep vein thrombosis (DVT), pulmonary embolism (PE).
  - Requirement for: vasopressors, systemic corticosteroids, or hemodialysis.
- Admission to an intensive care unit (ICU).
- Death.

7.5 Secondary Endpoints:

7.5.1 Key Secondary Endpoint:

First episode of PCR-positive nasal swab **and** ≥ 1 moderate or severe COVID-19, as defined under the primary endpoint.

7.5.2 Other Secondary Endpoints:

- ANY symptomatic SARS-CoV-2 infection, defined as: PCR-positive nasal swab **and** ≥ 1 of any of the following symptoms:
  - Fever.
  - New onset cough.
  - New onset or worsening of shortness of breath or difficulty breathing compared to baseline.
  - New onset fatigue.
  - New onset generalized muscle or body aches.
  - New onset headache lasting.
  - New loss of taste or smell.

  - Acute onset of sore throat, congestion or runny nose.
  - New onset nausea, vomiting or diarrhea.
- Neutralizing antibody titers from Immunogenicity Population at Days 0, 35 and Month 3.
- Serum IgG levels to SARS-CoV-2 S protein, hACE2 inhibition titers from Immunogenicity Population at Days 0, 35 and Month 3.
- Serum IgG levels to SARS-CoV-2 S protein, MN and hACE2 inhibition titers from Immunogenicity Population at Months 6, 12, 18 and 24.
- Description of course, treatment and severity of COVID-19 reported after a PCR-confirmed case via the Endpoint Form.
- Reactogenicity incidence and severity (mild, moderate or severe) recorded by all participants on their electronic patient-reported outcome diary application (eDiary) on days of vaccination and subsequent 6 days (total 7 days after each vaccine injection).
  - Reactogenicity endpoints include injection site reactions:
    - Pain.
    - Tenderness.
    - Erythema.
    - Swelling/induration.
  - Systemic reactions:
    - Fever.
    - Malaise.
    - Fatigue.
    - Arthralgia.
    - Myalgia.
    - Headache.
    - Nausea/vomiting.
- Incidence and severity of MAAEs through Day 49.
- Incidence and severity of unsolicited AEs through Day 49.
- Incidence and severity of MAAEs attributed to study vaccine, SAEs and AESIs through Month 12.
- Incidence and severity of SAEs, MAAEs attributed to study vaccine and AESIs during Month 12 through the EoS.
- Death due to any cause.

- Data points to be collected for healthcare requirements, utilization and medical assessments from participants who become ill on study will be defined in a separate substudy protocol.
- Antibodies to SARS-CoV-2 NP at Days 0 and 35, or Months 3, 6, 12, 18 and 24 will be used to determine natural infection and to determine the incidence of asymptomatic infection acquired during study follow-up.
- Antibodies to SARS-CoV-2 NP, regardless of whether the infection was symptomatic.

7.6 Exploratory Endpoints:

- Th1 or Th2 responses, eg, interleukin [IL]-2, IL-4, IL-5, IL-13, tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ) in whole blood and/or harvested peripheral blood mononuclear cell (PBMCs).
- Serum samples from a designated subset of up to approximately 4,500 Immunogenicity Population participants (non-overlapping with protocol designated Immunogenicity Population) to be transferred to National Institute of Allergy and Infectious Diseases (NIAID) for testing and analysis to determine correlates of risk and protection. Endpoints will be described in a separate statistical analysis plan (SAP) developed by external statistics groups (eg, COVID-19 Prevention Network [CoVPN], Operation Warp Speed [OWS]).
- Quantitative PCR tests may be performed on nasal swabs collected from this trial to assess whether vaccination impacts viral shedding.
- Next-generation sequencing of viral genomes detected in nasal swabs tested by PCR. These data are intended for future assessment across multiple clinical trials and for future publication. These data are not intended for initial regulatory submissions.

8 OVERALL STUDY DESIGN AND PLAN

8.1 Study Design Description

This is a Phase 3, randomized, observer-blinded, placebo-controlled study to evaluate the efficacy, safety and immunogenicity of SARS-CoV-2 rS with Matrix-M1 adjuvant in adult participants ≥ 18 years of age. Participants will be stratified by age group, and enrollment will occur concurrently within the 2 age strata, 18 to 64 years and ≥ 65 years.

The study will be a multicenter, global study with countries selected based on the expected COVID-19 epidemiology and healthcare system characteristics. Most study participants are expected to be enrolled in the United States (US). **Prioritization will be given to enrollment of individuals at high risk for COVID-19 by virtue of Black/African American or Native American race, Latinx ethnicity, co-morbid conditions (eg, obesity [BMI > 30 kg/m^2], chronic kidney or lung disease, cardiovascular disease and diabetes mellitus type 2) and life circumstances [living or working conditions involving known frequent exposure to SARS-CoV-2 or to densely populated circumstances [eg, nursing homes, factory or meat packing plants, healthcare providers, etc]).** (See Section 8.6 Recruitment and Retention for guidelines with respect to high-risk characteristics.)

After signing the informed consent form (ICF), including consent for the use of samples for future testing, potential participants may be screened within a window of up to 30 days, although it is expected that the majority of participants will be consented, enrolled and vaccinated on Day 0.

A total of up to approximately 30,000 participants ≥ 18 years of age will be assigned to their respective age stratum with no more than 3:1 representation in the 18-64 years:≥ 65 years groups. Participants will then be randomized in a 2:1 ratio via block randomization to receive 2 IM injections of SARS-CoV-2 rS + Matrix-M1 adjuvant or normal saline placebo as described in Table 2.

Study sites will be selected in the US and globally to ensure a diverse study population with respect to Black/African American or Native American race, Latinx ethnicity and age. Significant effort will be made to work with community engagement resources to ensure enrollment of underserved minorities.

While enrollment will be structured to ensure at least 25% of participants are ≥ 65 years of age, every effort will be made, due to the epidemiology of complications of COVID-19, to prioritize the enrollment of participants ≥ 65 years of age. Similarly, efforts will be made to prioritize the enrollment of participants < 65 years of age with co-morbidities (eg, obesity [BMI > 30 kg/m^2], chronic kidney or lung disease, cardiovascular disease and diabetes mellitus type 2), who are at higher risk of complications due to COVID-19. Participants will also be considered at high risk if their living or working conditions involve known frequent exposure to SARS-CoV-2 or to

densely populated circumstances (eg, nursing homes, factory or meat packing plants, healthcare providers, etc).

Table 2 Trial Vaccine Groups

Trial Vaccine Group	Number of Randomized Participants	2 Vaccinations	
		Day 0	Day 21 (+ 7 days)
SARS-CoV-2 rS (5 µg) + Matrix-M1 adjuvant (50 µg)	N up to 20,000 18-64 years: ≤ 15,000 ≥ 65 years: ≥ 5,000	X	X
Placebo (normal saline)	N up to 10,000 18-64 years: ≤ 7,500 ≥ 65 years: ≥ 2,500	X	X

Study vaccination regimens will comprise 2 IM injections (Day 0 and Day 21 + 7 days), preferably in alternating deltoids, with the trial vaccine assigned in a full dose injection volume of 0.5 mL. The dose level selected for evaluation is 5 µg SARS-CoV-2 rS adjuvanted with 50 µg Matrix-M1 based on optimal safety and immunogenicity observed in nonclinical and early clinical data. All vaccinations will be administered on an outpatient basis by qualified vaccine administrators in a way to maintain the blind as described in the Pharmacy Manual. Unblinded product will be managed by unblinded study site personnel who may administer study vaccine, if qualified to do so, but will not otherwise be involved in the study procedures or observations of participants.

Solicited AEs of reactogenicity, all subsequent AEs and COVID-19 symptomatology will be collected via participant reporting in the eDiary utilizing a smartphone application (see Section 10.4.3 for details). Participants who do not possess an appropriate device will be provided a device compatible with study requirements. All participants will be trained on the use of these applications at the initiation of the study (Day 0), and a Help Desk will be available 24 hours 7 days a week (24/7) for technical issues. For data entry issues, participants should contact the study site.

Overall safety assessments from Day 0 through the first 12 months of follow-up post final vaccination will include participant-recorded solicited (local and systemic reactogenicity) events through 7 days following each vaccination; unsolicited AEs and MAAEs through Day 49; and MAAEs attributed to vaccine, AESIs, SAEs and investigator-assessed targeted physical examination findings, including vital sign measurements through Month 12. During the second 12 months of follow-up post final vaccination, participants will be queried monthly regarding MAAEs attributed to study vaccine, AESIs and SAEs.

Blood samples for serologic assessments (anti-NP antibodies, IgG antibody to SARS-CoV-2 S protein, MN, and hACE2 inhibition) will be collected from all participants before the first

vaccination and at selected subsequent time points. Testing will be performed on a subset of collected sera from the Immunogenicity Population of up to approximately 1,200 participants from the active and placebo treatment groups that appropriately represent the study population in both age categories and countries designated at random by Novavax Biostatisticians who are blinded to treatment assignment. Participants who test positive for COVID-19 anti-NP antibodies and/or PCR-positive nasal swab at baseline, indicating previous SARS-CoV-2 infection, will have SARS-CoV-2 S protein immune responses analyzed but will not contribute to the primary (PP) immunogenicity or efficacy analyses. Results from the anti-NP positive and/or PCR-positive nasal swab participants will be assessed and reported separately. Whole blood samples for PBMC will be collected from a small subset of participants (< 100) representing both age strata and reasonably reflecting the demographic subgroups enrolled at selected study site(s) with the capacity to isolate PBMCs. These cells will be evaluated for cell-mediated immune responses to vaccine.

Participants will be provided with an oral thermometer on Day 0 and instructed to monitor their body temperature daily throughout the first 12 months of the study and to record temperature and any other relevant symptoms daily in their eDiary (see Section 10.4.3 for details). Participants who are noted during regular monitoring of the daily eDiary entries to not have reported temperature and symptoms for ≥ 7 days will be contacted by phone to assess clinical status and maintain engagement in the study. Electronic data capture (EDC) will be accomplished with an application installed on the participants' smartphone. Study participants who do not own smartphones compatible with these systems will be provided a device compatible with the applications. All participants will be trained on the use of these applications at the initiation of the study, and a Help Desk will be available 24/7 for technical issues. For data entry issues, participants should contact the study site.

Starting on Day 4, throughout the first 12 months of the study, when fever or other specified symptoms (see Table 3 for symptoms suggestive of COVID-19) are reported in the eDiary for at least 2 consecutive days for the same symptom, participants will be directed via the eDiary to begin daily nasal self-swabbing for PCR testing within 3 days of symptom onset at home for a total of 3 days and to initiate daily completion of the InFLUenza Patient-Reported Outcome (FLU-PRO) symptom reporting instrument for 10 days after COVID-19 symptom onset or until the participant experiences 2 consecutive asymptomatic days. Participants will be instructed at their enrollment visit on the methods of nasal self-swabbing for COVID-19 and completion of the FLU-PRO symptom reporting instrument. In addition, the eDiary will alert the study site to contact the participant to schedule the in-person Unscheduled Acute Illness Visit.

After the first day of home nasal swabbing, repeat nasal self-swabs should be obtained daily for a total of 3 days to ensure capture of intermittent shedding. The self-swabs obtained by the participant should be maintained according to directions provided in the 3-swab kit, and the

designated courier should be contacted to pick up the kit for shipping to the central lab, as directed.

At the in-person Unscheduled Acute Illness Visit, participants will be queried regarding AE symptoms, concomitant medications taken for these symptoms, undergo a targeted physical examination (to include O_2 saturation), if indicated, and have obtained by the study personnel a medically attended nasal swab, a blood sample for serologic testing and be trained on the use of the portable pulse oximeter that they will take home with them. Medically attended swabs collected at the Unscheduled Acute Illness Visit will be processed at the study site according to established procedures as described in the Laboratory Manual.

Completion of the FLU-PRO reporting instrument and O_2 saturation (at rest and following mild exercise, defined as walking around the room for 1 minute) will be captured daily in the eDiary for 10 days after COVID-19 symptom onset or until the participant experiences 2 consecutive asymptomatic days.

Study participants whose home nasal self-swab and/or medically attended nasal swabs are confirmed at the central laboratory to be PCR-positive for SARS-CoV-2 at the Unscheduled Acute Illness Visit will be contacted by the study site to arrange an Unscheduled Convalescent Visit. The Unscheduled Convalescent Visit will occur approximately 1 month (or as soon thereafter, as feasible) after the onset of the PCR-confirmed case of COVID-19 at the Unscheduled Acute Illness Visit to assess status of AEs, record the clinical course of the disease on the Endpoint Form and obtain a blood sample for convalescent serologic testing. Pulse oximeters should be returned to the study site at this visit.

An acute illness clinically consistent with COVID-19 should be based on the presence of any of the symptoms enumerated below (Table 3) that are reported for at least 2 consecutive days and, more specifically, in the primary endpoint (Section 7.4). In the case of rapid decompensation to a severe COVID-19 case, hospital or post-mortem data can be used for virologic confirmation of positive cases, but every effort should be made to send a duplicate swab to the central lab for the study to be included in the primary analysis. Hospitalization records and/or data should be obtained as feasible to ensure adequate characterization of the severity of COVID-19.

Table 3 Symptoms Suggestive of COVID-19

Symptoms Suggestive of COVID-19
Fever (body temperature > 38.0° C, in the absence of other symptoms) or chills
New onset or worsening of cough compared with baseline
New onset or worsening of shortness of breath or difficulty breathing over baseline
Severe fatigue
New onset generalized muscle or body aches
Headache
New loss of taste or smell
Sore throat
Congestion or runny nose
Nausea or vomiting
Diarrhea

The study will consist of a screening period up to 30 days prior to Day 0); vaccination days (Days 0 and 21 + 7 days); outpatient study visits on Days 0, 21 (+ 7 days), 35 (+ 7 days), and Month 3 (+ 15 days); and at 6 months (± 15 days) after the last vaccination. Additional study visits for blood draws will occur at 12 (± 15 days), 18 (± 30 days) and 24 months (± 30 days) after the last vaccination. In addition to the aforementioned Unscheduled Acute Illness and Unscheduled Convalescent Visits, an Unscheduled General Visit may be conducted by study personnel in the event of a general medical issue other than COVID-19 symptomatology, if needed. An EoS visit will be recorded for all study participants at approximately 24 months (± 30 days) after their last vaccination or at their last visit on study. Should participants decide to terminate early, an EoS telephone visit will occur to collect the maximum safety data and blood sample, if possible. All study participants will be encouraged to continue in follow-up for safety and reported COVID-19 cases. The duration of the study, excluding screening, is approximately 24 months for each participant.

This protocol has extensive safety monitoring in place. Safety is monitored daily by the ICON Medical Monitor, Novavax Pharmacovigilance and Safety Surveillance Physicians, and routinely by the 2019nCoV-301 Protocol Safety Review Team (PSRT). In addition, an independent Data and Safety Monitoring Board (DSMB) periodically reviews study data, including unblinded study data if/when needed.

If this vaccine or another is demonstrated to be safe and efficacious and approved by regulatory authorities, participants for whom the new vaccine is recommended and available will be counseled with respect to their options. These participants may be offered the opportunity to be unblinded so that those who received placebo may be offered the Novavax vaccine or another product, as appropriate, outside the protocol procedures. Participants who are unblinded and receive an active vaccine in this manner will be censored in the final analysis at the time of

unblinding but will be strongly encouraged to remain in safety follow-up as defined in this protocol.

A centralized DSMB will be established in collaboration with NIH, NIAID, Biomedical Advanced Research and Development Authority (BARDA) and Novavax according to the charter dictated by the participating groups. This group will review interim unblinded data on a monthly basis and make recommendations with respect to safety and emerging efficacy. Furthermore, the DSMB may recommend that the trial be terminated or that specific groups be withdrawn from the study, if any subgroup manifests serious or widespread side effects. The DSMB will be informed immediately by the ICON unblinded statistician if the pre-specified stopping boundary is met, indicating that the vaccine causes harm by increasing the rate of mild, moderate or severe COVID-19. In addition, the DSMB will monitor the study for high vaccine efficacy or for futility to detect vaccine activity.

An in-person, unscheduled visit to the study site or at the participant's home may replace remote reporting and testing, if medically indicated and acceptable based on the ongoing pandemic and participant containment requirements and participant consent. Participants who have failed to complete their daily temperature and/or symptom reports in their eDiary for ≥ 7 days will receive a call from the study site to remind them to collect illness symptoms.

Endpoint collection will be obtained using hospital-derived information as reported on SAE forms or, if possible, electronic medical records. Consent for access to hospital records and data will be obtained at the time of entry into the study.

Modifications to follow-up procedures to comply with evolving regulations and recommendations due to the ongoing pandemic will be incorporated as needed to ensure appropriate data collection while maintaining health and safety of participants, communities and study personnel.

8.2 Discussion of Study Design

This is a Phase 3, multinational, multicenter, randomized, observer-blinded, placebo-controlled study to evaluate the efficacy, safety and immunogenicity of 5 µg SARS-CoV-2 rS with 50 µg Matrix-M1 adjuvant in up to approximately 30,000 adult participants ≥ 18 years of age at substantial risk of exposure to and infection with SARS-CoV-2 infection. A placebo control is considered ethical, as there are no vaccines or other preventive agents approved for SARS-CoV-2. In this study, participants will be stratified by age group (18 to 64 years and ≥ 65 years) and randomized in a 2:1 ratio via block randomization to receive 2 IM injections of 5 µg SARS-CoV-2 rS adjuvanted with 50 µg Matrix-M1 or normal saline placebo on Days 0 and 21 + 7 days. An unequal randomization schema (2:1) was selected to expose more participants to active vaccine, and statistical modeling showed satisfactory statistical power for this randomization ratio. Such an approach should not negatively impact the power of the study, given the large sample size and prevalence of active disease.

This study will be multinational and multicenter, with countries selected based on the expected COVID-19 epidemiology and healthcare system characteristics. Study sites will be selected globally, including in the US, to ensure a diverse study population is represented with respect to Black/African American and Native American race and Latinx ethnicity. At least 25% of the study population is intended to be in the ≥ 65 years age group. Most study participants are expected to be enrolled in the US. **Prioritization will be given to enrollment of individuals at high risk for COVID-19 by virtue of Black/African American or Native American race, Latinx ethnicity, co-morbid conditions (BMI > 30 kg/m^2, chronic kidney or lung disease, cardiovascular disease, diabetes mellitus type 2) and by life circumstance (living or working conditions involving known frequent exposure to SARS-CoV-2 or to densely populated circumstances [eg, nursing homes, factory or meat packing plants, healthcare providers, etc).** (See Section 8.6 Recruitment and Retention for guidelines with respect to high-risk characteristics.) Much of the clinical data will be collected using EDC systems installed on participants' smartphones. Participants who do not own a device that can accommodate this form of patient-reported outcomes will be provided with a compatible device to use for the study. Care will be taken to thoroughly train all participants in the use of the application on their electronic devices, and a 24/7 Help Desk will be available for technical issues, as needed. For data entry issues, participants should contact the study site. Lastly, this study will follow participants for 24 months to explore long-term efficacy, safety, and immunogenicity of Matrix-M1 adjuvanted SARS-CoV-2 rS.

8.2.1 End of Study Definition

A participant is considered to have completed the study if they have completed all phases of the study, including the EoS visit.

The end of the study is defined as the date of the last EoS visit for the last participant in the study globally.

8.2.2 Trial Vaccine After the End of Study

If this vaccine or another is demonstrated to be safe and efficacious and approved by regulatory authorities, participants for whom the new vaccine is recommended and available will be counseled with respect to their options. These participants may be offered the opportunity to be unblinded so that those who received placebo may be offered the Novavax vaccine or another product, as appropriate, outside the protocol procedures. Participants who are unblinded and receive an active vaccine in this manner will be censored in the final analysis at the time of unblinding but will be strongly encouraged to remain in safety follow-up as defined in this protocol.

8.3 Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

8.3.1 Inclusion Criteria

Each participant must meet all of the following criteria to be enrolled in this study:

1. Adults≥ 18 years of age at screening who, by virtue of age, race, ethnicity or life circumstances, are considered at substantial risk of exposure to and infection with SARS-CoV-2. (See Section 8.6, Recruitment and Retention for guidelines with respect to high-risk characteristics.)
2. Willing and able to give informed consent prior to study enrollment and to comply with study procedures.
3. Participants of childbearing potential (defined as any participant who has experienced menarche and who is NOT surgically sterile [ie, hysterectomy, bilateral tubal ligation, or bilateral oophorectomy] or postmenopausal [defined as amenorrhea at least 12 consecutive months]) must agree to be heterosexually inactive from at least 28 days prior to enrollment and through 3 months after the last vaccination OR agree to consistently use a medically acceptable method of contraception from at least 28 days prior to enrollment and through 3 months after the last vaccination.
4. Is medically stable, as determined by the investigator (based on review of health status, vital signs [to include body temperature], medical history, and targeted physical examination [to include body weight]). Vital signs must be within medically acceptable ranges prior to the first vaccination.
5. Agree to not participate in any other SARS-CoV-2 prevention trial during the study follow-up.

8.3.2 Exclusion Criteria

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

1. Unstable acute or chronic illness. Criteria for unstable medical conditions include:
   a. Substantive changes in chronic prescribed medication (change in class or significant change in dose) in the past 2 months.
   b. Currently undergoing workup of undiagnosed illness that could lead to diagnosis of a new condition.

   Note: Well-controlled human immunodeficiency virus [HIV] with undetectable HIV RNA [< 50 copies/mL] and CD4 count > 200 cells/µL for at least 1 year, documented within the last 6 months, is NOT considered an unstable chronic illness.
2. Participation in research involving an investigational product (drug/biologic/device) within 45 days prior to first study vaccination.
3. History of a previous laboratory-confirmed diagnosis of SARS-CoV-2 infection or COVID-19.
4. Received influenza vaccination or any other adult vaccine within 4 days prior to or within 7 days after either study vaccination.
5. Autoimmune or immunodeficiency disease/condition (iatrogenic or congenital) requiring ongoing immunomodulatory therapy that is judged to cause significant immunocompromise.

   NOTE: Stable endocrine disorders (eg, thyroiditis, pancreatitis), including stable diabetes mellitus with no history of diabetic ketoacidosis) are NOT excluded.
6. Chronic administration (defined as > 14 continuous days) of immunosuppressant, systemic glucocorticoids, or other immune-modifying drugs within 90 days prior to first study vaccination.

   NOTE: An immunosuppressant dose of glucocorticoid is defined as a systemic dose ≥ 20 mg of prednisone per day or equivalent. The use of topical, inhaled, and nasal glucocorticoids is permitted. Topical tacrolimus and ocular cyclosporin are permitted.
7. Received immunoglobulin, blood-derived products, or immunosuppressant drugs within 90 days prior to first study vaccination.
8. Active cancer (malignancy) on chemotherapy that is judged to cause significant immunocompromise within 1 year prior to first study vaccination (with the exception of malignancy cured via excision, at the discretion of the investigator).
9. Any known allergies to products contained in the investigational product.

10. Participants who are breastfeeding, pregnant or who plan to become pregnant within 3 months following last study vaccination.
11. Any other condition that, in the opinion of the investigator, would pose a health risk to the participant if enrolled or could interfere with evaluation of the trial vaccine or interpretation of study results.
12. Study team member or first-degree relative of any study team member (inclusive of Sponsor, and study site personnel involved in the study).
13. Current participation in any other COVID-19 prevention clinical trial.

8.3.3 Other Considerations:

Participants meeting the following criterion may be delayed for subsequent vaccination:

- Respiratory symptoms in the past 3 days (ie, body temperature of > 38.0ºC, cough, sore throat, difficulty breathing). Participant may be vaccinated when all symptoms have been resolved for > 3 days. Out of window vaccination is allowed for this reason.

8.4 Prohibited Medications

Prescription medications for the prevention of COVID-19 are prohibited during this study. Seasonal influenza vaccination or any other adult vaccine within 4 days prior to or within 7 days after either study vaccination to avoid confounding reactogenicity observations.

8.5 Lifestyle Considerations

There are no lifestyle restrictions.

8.6 Strategies for Recruitment and Retention

All recruitment material will be approved by an Independent Ethics Committee (IEC) or Institutional Review Board (IRB) prior to implementation.

In addition to at least 25% participants ≥ 65 years of age, every effort must be made to recruit and enroll racially and ethnically diverse populations that appropriately reflect the populations most impacted by the COVID-19 pandemic. Additionally, potential participants of any eligible age who reflect the baseline co-morbidities that are most likely to suffer severe COVID-19 (eg, obesity [BMI > 30 kg/m^2], chronic kidney or lung disease, cardiovascular disease and diabetes mellitus type 2) should be prioritized for enrollment in the study with a goal of ≥ 25% of participants with high-risk co-morbidities. Participants will also be considered at high risk if their living or working conditions involve known frequent exposure to SARS-CoV-2 or to densely populated circumstances (eg, nursing homes, factory or meat packing plants, healthcare providers, etc).

Specifically, study sites should also target **overall enrollment of at least 15% Black/African Americans, 10% to 20% Latinx Americans and, where feasible, 1% to 2% Native Americans.** Demographic characteristics and baseline co-morbidities will be monitored during the enrollment period to ensure the desired population is being recruited.

Retention of participants and capture of endpoint COVID-19 will be facilitated by regular monitoring of the daily eDiary so that participants who are noted to not have reported temperature and symptoms for ≥ 7 days will be contacted by phone to assess clinical status and maintain engagement in the study. Constant centralized monitoring of the electronic database will enable identification of any potential issues related to participant retention, including study participants who have missed regular reporting.

8.7 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to trial vaccine/entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Participants who withdraw, are withdrawn or terminated from this study, or are lost to follow-up after signing the ICF but prior to first study vaccination may be replaced. Participants who receive trial vaccine and subsequently withdraw, are discontinued from further vaccination, are terminated from the study, or are lost to follow-up will not be replaced.

8.8 Trial Vaccine Discontinuation and Participant Discontinuation/Withdrawal

8.8.1 Trial Vaccine Discontinuation

The investigator may withhold the second vaccination from a participant in the study if the participant:

1. Is noncompliant with the protocol.
2. Experiences an SAE or intolerable AE(s) for which vaccination is not advised by the investigator.
3. Pregnancy (discontinuation of further vaccination is required).

The investigator must determine the primary reason for the participant's premature discontinuation of trial vaccine and record this information on the treatment disposition electronic case report form (eCRF) page. The investigator and study staff must discuss with the participant, the need for the participant's continued participation for safety follow-up according to the study visit schedule. Participants who discontinue due to an AE should be followed to resolution of the AE or determination that it is a chronic condition.

The appropriate personnel from the study site in consultation with ICON Clinical Research Ltd. will assess whether trial vaccine should be discontinued for any participant whose treatment code has been broken inadvertently for any reason.

The investigator must also contact the interactive web response system (IWRS) to register the participant's discontinuation from trial vaccine.

8.8.2 Study Temporary Discontinuation/Vaccine Pause

Safety issues, such as the following, will be reviewed by the independent DSMB during their periodic data reviews, and a determination made regarding the continuation of vaccination in the study:

- An unacceptable imbalance of more SAEs and/or suspected unexpected serious adverse reactions (SUSARs) in the active vaccine treatment group.
- Moderate-to-severe COVID-19 occurring in statistically more vaccine recipients than placebo recipients, as might be suggestive of vaccine-enhanced disease, see Section 12.5.

Continued follow-up of all enrolled participants will be maintained to fully characterize the safety profile.

8.8.3 Withdrawal of Participants

8.8.3.1 Discontinuation/Withdrawal by Participant

Participants may voluntarily withdraw consent to participate in the study for any reason at any time or may be withdrawn at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

If a participant withdraws consent, the investigator must make every effort to determine the primary reason for this decision and record this information on the treatment disposition eCRF page. If the participant decides to completely withdraw from the study (refuses any further study participation or contact), all study participation for that participant will cease and data to be collected at subsequent visits will be considered missing. Further attempts to contact the participant are not allowed unless safety findings require communication or follow-up.

Participants may refuse further procedures (including 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, etc).

8.8.3.2 Discontinuation/Withdrawal by Investigator

The investigator can also withdraw a participant upon the request of the Sponsor or if the Sponsor terminates the study. Upon the occurrence of an SAE or intolerable AE, the investigator may confer with the Sponsor before the second vaccination. Participants who become pregnant on-study will be followed for the duration of the pregnancy to document the pregnancy outcome.

8.8.3.3 Discontinuation/Withdrawal by Sponsor (Study Halting Rules)

Although Novavax has every intention of completing the study, they reserve the right to discontinue the study at any time for clinical or administrative reasons. The EoS is defined as the date on which the last participant completes the last study visit (including the EoS visit). Any additional long-term follow-up that is required for monitoring of the resolution of an AE or finding may be appended to the clinical study report.

In addition, the study will be discontinued if Novavax, Inc. or designee, including through DSMB recommendation, judges it necessary for medical, safety, or business reasons consistent with applicable laws, regulations and GCP.

8.9 Lost to Follow-up

Participants will be asked to provide an emergency contact at the time of the Informed Consent process. All reasonable efforts, including contact of emergency contact, must be made to locate participants to determine and report their ongoing status. Lost to follow-up is defined by the inability to reach the participant after a minimum of 3 documented phone calls, text messages, faxes or emails (not performed on the same day), as well as a lack of response by the participant

to one registered mail letter. All attempts should be documented in the participant's source documents and/or medical records. If it is determined that the participant has died, the study site will use permissible local methods to obtain the date and cause of death and as much other information as can be obtained, including post-mortem reports.

Data that would have been collected at subsequent visits will be considered missing.

8.10 Discontinuation of Study Sites

Study site participation may be discontinued if Novavax, Inc. or designee, the investigator or IRB/IEC of the study site judges it necessary for medical or safety reasons consistent with applicable laws, regulations and Good Clinical Practice (GCP).

9 STUDY TREATMENT

The following supplies will be used for vaccination in the study:

- SARS-CoV-2 rS (5 µg) adjuvanted with Matrix-M1 (50 µg)
- Placebo (normal saline)

Formulation: SARS-CoV-2 rS is a liquid solution formulated in [redacted] and diluted with the same to specified concentrations co-formulated with Matrix-M1 adjuvant that also contains [redacted].

Further details on the trial vaccine can be found in the SARS-CoV-2 rS IB and description of the presentation are defined in the Pharmacy Manual.

9.1 Administration of Study Treatment(s)

The vaccine should be drawn into a syringe on the day of administration by a qualified and unblinded member of study site personnel, and the vaccine should be administered according to standard practice by qualified study site personnel in a way to maintain the blind, as directed in the Pharmacy Manual.

The study vaccination regimen will comprise 2 IM injections (Day 0 and Day 21 + 7 days) of injection volume of 0.5 mL in the deltoid. It may be preferred to administer the 2 doses in alternate arms, but this is not required. The dose level is 5 µg SARS-CoV-2 rS adjuvanted with 50 µg Matrix-M1 based on data from earlier nonclinical and early clinical trials.

All vaccinations will be administered on an outpatient basis by qualified vaccine administrators in a way to maintain the blind. Unblinded product will require unblinded study site personnel who may administer the study vaccine if qualified to do so, but will not otherwise be involved in the study procedures or observations of participants.

9.2 Study Treatment Packaging and Labelling

9.2.1 Packaging and Labelling

Novavax, Inc. will provide adequate quantities and appropriate labelling of SARS-CoV-2 rS with Matrix-M1 adjuvant and PCI Pharma Services will ensure distribution to the study sites from a designated depot. Sodium chloride, 0.9% for injection (US Pharmacopeia, sterile or equivalent) is commercially available and will be supplied by PCI Pharma Services. The clinical unit pharmacy or equivalent will prepare the clinical trial materials (vaccine or placebo) for each participant. Detailed instructions for the handling of trial vaccine vials will be provided in a separate Pharmacy Manual.

9.2.2 Storage

All trial vaccines must be stored according to the labelled instructions in a secure cabinet or room with access restricted to necessary clinic personnel. The study site will be required to keep a temperature log to establish a record of compliance with storage conditions.

The SARS-CoV-2 rS vaccine with Matrix-M1 adjuvant should be stored at 2°C to 8°C in a secured location. DO NOT FREEZE.

9.3 Vaccine Compliance

All doses of the trial vaccine should be administered in the clinical unit under direct observation of clinic personnel and recorded in the eCRF but may need to occur outside of the study site depending on the pandemic situation (eg, home vaccinations). Home vaccination visits must have adequate oversight for issues associated with immediate severe reactions. Clinic personnel will confirm that the participant has received the entire dose. The location (right or left arm), date, and timing of all doses of trial vaccine will be recorded in the participants' eCRF. If a participant is not administered trial vaccine, the reason for the missed dose will be recorded.

9.4 Prior Vaccinations and Concomitant Therapy

Administration of non-study medications, therapies, or vaccines will be recorded in the eCRF. Concomitant medications will include all medications (including vaccines) taken by the participant from the time of signing the ICF through Day 49, and all medications taken by the participant for treatment of a reportable SAEs, MAAEs attributed to vaccine or AESIs from Day 50 through EoS (or through the early termination visit, if prior to EoS). Prescription and over-the-counter drugs, as well as herbals, vitamins, and supplements, will be included when used for the above indications.

Prohibited medications are detailed in Section 8.4.

9.5 Blinding and Randomization of Study Treatment(s)

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

Within each study site, participants will be assigned to the appropriate age stratum (18-64 years or ≥ 65 years) and randomized to study treatment according to a list produced by ICON. Prior to production, the randomization specification will be reviewed and agreed by the study team (Sponsor and ICON). As block size is considered potentially unblinding information, it will be known to the Study Biostatistician only.

An IWRS will be responsible for the allocation of randomization numbers to individual participants. Randomization will take place at baseline after confirmation that the participant meets the inclusion/exclusion criteria. Participants will be randomized in a 2:1 ratio to receive either SARS-CoV-2 rS with Matrix-M1 adjuvant or placebo, administered via IM route. A copy of the randomization code with true treatment allocations will be held by ICON during the study. Another randomization list (containing treatment) will be provided to clinical supplies.

9.6 Procedure for Breaking the Randomization Code

A participant's vaccine assignment will not be revealed to the study site study team until the end of the study unless medical treatment of the participant depends on knowing the trial 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 without communication with the Sponsor, although communication with ICON or the Sponsor must occur as soon thereafter as possible.

Prior to unblinding, or as soon thereafter as possible, the investigator should contact the ICON Medical Monitor to discuss the medical emergency and the reason for revealing the actual vaccine received by that participant. Emergency code breaks are performed using the IWRS. Reasons for vaccine unblinding 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 IWRS 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 fax or email confirming this information. The system will automatically inform the PSRT, ICON Site Monitor, the ICON Medical Monitor, and the ICON Project Manager 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 IWRS 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, trial 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.

In addition to the aforementioned emergency situations where the blind may be broken, the data will also be unblinded to the ICON unblinded statistician at specified time points for planned interim reviews by the DSMB prior to study completion.

9.7 Study Treatment Accountability

The investigator (or delegate) will maintain accurate records of receipt of all trial vaccine, including dates of receipt. Accurate records will be kept regarding when and how much trial vaccine is dispensed and used by each participant in the study. Reasons for departure from the expected dispensing regimen must also be recorded. At the completion of the study, and to satisfy regulatory requirements regarding trial vaccine accountability, all used and unused trial vaccines will be reconciled and retained or destroyed according to applicable regulations. No trial vaccine will be destroyed until authorized in writing by the Sponsor.

10 STUDY ASSESSMENTS AND PROCEDURES

Before performing any study procedures, all potential participants will sign an ICF and provide an emergency contact as outlined in Section 13.2. Participants will undergo study procedures at the time points specified in the SoA (Table 1).

Due to the ongoing pandemic, recent national regulatory and local IEC/IRB and public health guidance may be applied at the study site locations regarding alterations in the ability of study participants to attend a study site for protocol-specified visits, with the study site's investigator being allowed to conduct safety assessments (eg, telephone, email or text message contact, alternative location for assessment, including local laboratories or home visits) when necessary and feasible, as long as protective procedures ensure such visits are conducted according to appropriate guidelines sufficient to assure the safety of study participants. Serum samples may be drawn using local phlebotomy services, home health, or other modalities if study site visits cannot occur. Vaccination visits must have adequate oversight for issues associated with immediate severe reactions but may need to occur outside of the study site depending on the pandemic situation (eg, home vaccinations).

10.1 Efficacy Assessments

10.1.1 Active Surveillance for COVID-19

Participants will be provided with a thermometer and instructed to monitor their body temperature daily throughout the study and to record body temperature and any other relevant symptoms daily in their eDiary (see Section 10.4.3 for details). Participants who are noted during regular monitoring of the daily eDiary entries to not have reported temperature and symptoms for ≥ 7 days will be contacted by phone to assess clinical status and maintain engagement in the study.

Symptoms of severe COVID-19 should be reported as an SAE (important medical event) beginning on Day 0 following the first study vaccine administration (Section 7.4) and appropriate medical care should be sought. Starting on Day 4, throughout the first 12 months of the study, when fever or other specified symptoms (see Table 3 for symptoms suggestive of COVID-19) are reported in the eDiary for at least 2 consecutive days for the same symptom, participants will be directed via the eDiary to begin daily nasal self-swabbing for PCR testing within 3 days of symptom onset at home for a total of 3 days and to initiate daily completion of the FLU-PRO symptom reporting instrument for 10 days after COVID-19 symptom onset or until the participant experiences 2 consecutive asymptomatic days. Participants will be instructed at their enrollment visit on the methods of nasal self-swabbing for COVID-19 and completion of the FLU-PRO symptom reporting instrument. In addition, the eDiary will alert the study site to contact the participant to schedule the in-person Unscheduled Acute Illness Visit.

After the first day of home nasal swabbing, repeat nasal self-swabs should be obtained daily for a total of 3 days to ensure capture of intermittent shedding. The self-swabs obtained by the participant should be maintained according to directions provided in the 3-swab kit, and the designated courier should be contacted to pick up the kit for shipping to the central lab, as directed.

Participants may also be evaluated, and appropriate swab and blood samples obtained, by other methods to ensure the appropriate level of medical care (eg, telemedicine, hospital/COVID-19 ward records, home visits) based on ongoing pandemic and participant containment requirements.

10.1.2 Unscheduled Acute Illness and Convalescent Visits

At the in-person Unscheduled Acute Illness Visit, participants will be queried regarding AE symptoms, concomitant medications taken for these symptoms, undergo a targeted physical examination (to include O_2 saturation), if indicated, and have obtained by the study personnel a medically attended nasal swab, a blood sample for serologic testing and be trained on the use of the portable pulse oximeter that they will take home with them. Medically attended swabs collected at the Unscheduled Acute Illness Visit will be processed at the study site according to established procedures as described in the Laboratory Manual.

All Unscheduled Acute Illness Visits and assessments performed during the visits will be recorded in the participant's eCRF. Laboratory samples collected for the purpose of routine medical care may not be reimbursed by the clinical trial.

Study participants whose home nasal self-swab and/or medically attended nasal swabs are confirmed at the central laboratory to be PCR-positive for SARS-CoV-2 at the Unscheduled Acute Illness Visit will be contacted by the study site to arrange an Unscheduled Convalescent Visit. The Unscheduled Convalescent Visit will occur approximately 1 month (or as soon thereafter, as feasible) after the onset of the PCR-confirmed case of COVID-19 at the Unscheduled Acute Illness Visit to assess status of AEs, record the clinical course of the disease on the Endpoint Form and obtain a blood sample for convalescent serologic testing. Pulse oximeters should be returned to the study site at this visit.

10.1.3 Nasal Swabs for Virus Detection

Nasal swabs of the anterior nares will be obtained at the study site on Day 0 (prior to study vaccination) and at the Unscheduled Acute Illness Visit.

Participants who experience an SAE of severe COVID-19 any time after Day 0 should, if at all possible, have a nasal swab obtained (by site personnel or other healthcare personnel) to be sent by the study site to the study central laboratory. Such a swab, if obtained, will constitute the medically attended nasal swab recorded on the Acute Illness Visit form.

Starting on Day 4, throughout the first 12 months of the study, when fever or other specified symptoms (see Table 3 for symptoms suggestive of COVID-19) are reported in the eDiary for at least 2 consecutive days for the same symptom, participants will be directed via the eDiary to begin daily nasal self-swabbing for PCR testing within 3 days of symptom onset at home for a total of 3 days to ensure capture of intermittent shedding. The self-swabs obtained by the participant should be maintained according to directions provided in the 3-swab kit, and the designated courier should be contacted to pick up the kit for shipping to the central lab, as directed. Medically attended swabs collected at the Unscheduled Acute Illness Visit will be processed at the study site according to established procedures.

Participants will be instructed at their enrollment visit on the method of self-swabbing for COVID-19 and procedure for arranging transport of swabs to the central lab. Quantitative PCR may be performed on PCR-positive swabs to assess viral load and sequencing of viral genetic material detected in nasal swab PCR testing to evaluate viral mutations. No participant genetic material will be sequenced or otherwise tested.

10.1.4 FLU-PRO

Participants will be instructed at their enrollment visit on the completion of the FLU-PRO symptom questionnaire. A Help Desk will be available 24/7 for technical issues. For data entry issues, participants should contact the study site.

Starting on Day 4, throughout the first 12 months of the study, when fever or other specified symptoms (see Table 3 for symptoms suggestive of COVID-19) are reported in the eDiary for at least 2 consecutive days for the same symptom, participants will be directed via the eDiary to initiate daily completion of the FLU-PRO symptom reporting instrument for 10 days after COVID-19 symptom onset or until the participant experiences 2 consecutive asymptomatic days.

The FLU-PRO will be completed by participants electronically via an application installed on the participants' smartphone or a similar device provided by the study for individuals who do not own a smartphone. The FLU-PRO questionnaire was designed to standardize and comprehensively assess symptoms associated with various viruses across multiple body systems over the course of influenza disease, and has been adapted for COVID-19, within and across subgroups. It was developed using qualitative and quantitative methods consistent with scientific measurement standards and US Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidelines for clinical outcome assessments.

FLU-PRO has been tested and used in studies of influenza, influenza-like illness, rhinovirus, enterovirus, and more recently COVID-19. To date, the FLU-PRO has been completed by over 4,000 participants between 12 to 81 years of age with adherence rates over 90%.

FLU-PRO is a 32-item instrument that assesses severity of symptoms of influenza and influenza-like illness across 6 body systems (nose, throat, eyes, chest/respiratory, gastrointestinal, and

body/systemic), with at least 2 additional symptoms (ie, acute loss of sense of smell and/or taste) added that have been associated with COVID-19. In the current study, participants will complete the FLU-PRO daily for 10 days after onset or until the participant experiences 2 asymptomatic days. Each question is brief (sign or symptom only with severity rating) and the entire questionnaire takes under 4 minutes to complete. The instrument also provides data on the presence/absence and severity of symptoms, symptom profiles, and change over time; these are the data points that will be used in this trial. It is noted that for purposes of this study the FLU-PRO diary is being used only for collection of symptoms and severity; there is no intention of using the FLU-PRO scores in any analyses.

10.1.5 Oxygen Saturation Monitoring

At the Unscheduled Acute Illness Visit, O_2 saturation (at rest and following mild exercise, defined as walking around the room for 1 minute) will be measured using a pulse oximeter. The study sites will provide a portable pulse oximeter for recording O_2 saturation (at rest and following mild exercise) daily in the eDiary and train the participant on the use of the pulse oximeter under both conditions (rest and mild exercise). The device will be accompanied by careful instructions for use and recording of O_2 saturation in the eDiary and who to contact for assistance if the device malfunctions. The purpose of the monitoring of O_2 saturation is to enhance the assessment of severity and progression of COVID-19, as well as to ensure that participants are adequately informed with respect to their medical condition and are warned to seek medical care when needed.

10.2 Immunogenicity Assessments

Blood samples for serologic assessments (anti-NP antibodies, IgG antibody to SARS-CoV-2 S protein, MN, and hACE2 inhibition) will be collected from all enrolled participants before vaccination and at the appointed time points following vaccination (see Table 1).

Immune measurements (IgG antibody to SARS-CoV-2 S protein, MN, and hACE2 inhibition) will be performed on a subset of collected sera from the Immunogenicity Population of up to approximately 1,200 participants from the active and placebo treatment groups that appropriately represent the study population in both age categories and countries, designated at random by Novavax Biostatistics who are blinded to treatment assignment. Testing for anti-NP antibodies will be performed on serum from up to all enrolled participants to evaluate prior infection at baseline and new infection (including asymptomatic infection) across the duration of the study. Additional testing relevant to coronavirus infection and epidemiology may be identified during or after the trial that may be performed on banked sera. Whole blood samples for PBMC testing for cell-mediated immunity will be collected from a small subset of participants (< 100) representing both age strata and reasonably reflecting the demographic subgroups enrolled at selected study site(s) with the capacity to isolate PBMCs. These study site(s) will be identified prior to trial initiation.

Aliquots of all collected samples from this study may be retained for use in future relevant research for a maximum of 25 years (starting from the date at which the last participant had the last study visit), unless local rules, regulations, or guidelines require different timeframes or different procedures, in accord with participant consent.

10.3 Safety Assessments

The timing and frequency of all safety assessments are listed in the SoA (Table 1). Solicited and unsolicited AEs will be graded for severity using the provided criteria. Recording of solicited and unsolicited AEs will be conducted by EDC. AESIs, including potential immune-mediated medical conditions (PIMMC) and AESIs specific to complications of potential disease enhancement for COVID-19 will also be monitored (see Appendix 2 for details).

The timing and frequency of safety assessments are described in Table 1.

10.3.1 Definitions

The definition of AEs, treatment-emergent adverse events (TEAEs), AESIs and SAEs is given below. The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of and AE, SAE or AESI and remain responsible for following up AEs that are serious, considered related to the trial vaccine or study procedures, or that causes the participant to discontinue the trial vaccine/study.

10.3.1.1 Adverse Events

An AE is defined as any untoward medical occurrence in a participant, or clinical investigation participant administered a pharmaceutical product, and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom or disease temporally associated with the use of a medicinal (investigational) product, regardless of whether related to the medicinal (investigational) product.

10.3.1.2 Events Meeting the AE Definition

- Any abnormal laboratory test results or other safety assessments (eg, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgement of the investigator (ie, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after trial vaccine administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

- "Lack of efficacy" or "failure of expected pharmacological action" *per se* will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

10.3.1.3 Serious Adverse Event

An SAE is defined as any untoward medical occurrence that:

- Results in death. The cause of death is the AE, death is an outcome.
- Is life-threatening. The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- Requires inpatient hospitalization or prolongs existing hospitalization. In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether 'hospitalization' occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an SAE.
- Results in persistent or significant disability/incapacity. The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect.
- Is an important medical event. Important medical events that may not result in death, be life-threatening or require hospitalization may be considered a serious adverse drug experience, when based on appropriate medical judgement, they may directly jeopardize the participant or the participant may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
- Events of severe COVID-19 (see Section 7.4) constitute important medical events for this study. Events that may have, in a different hypothetical situation, been life-threatening,

but did not pose an immediate life-threatening condition to the given study participant are not considered SAEs.

10.3.1.4 Treatment-Emergent Adverse Event

TEAEs are defined as any AE occurring or worsening on or after the first dose of trial vaccine.

10.3.1.5 Adverse Event of Special Interest

Participants will be assessed for diagnosis of an AESI at all study contacts. AESIs include PIMMCs, AEs specific to complications of COVID-19 (listed in Appendix 2), or other potential AEs that may be determined at any time by regulatory authorities as additional information concerning COVID-19 is obtained. Given the concern for "cytokine storm", an AESI of cytokine release syndrome will be included as an AE specific to COVID-19. Listings of AESI are presented in Appendix 2.

An AESI must be reported as if it is an SAE (Section 10.3.6).

10.3.1.6 Medically Attended Adverse Events

An MAAE is defined as an AE that leads to an unscheduled visit to a healthcare practitioner.

10.3.1.7 Reactogenicity Symptoms

On vaccination days, participants will remain in clinic (or under observation) for at least 30 minutes to be observed for any severe reactogenicity. Site specific local (arm) and general systemic reactogenicity reactions including start and stop dates will be recorded and the investigator will apply a standard toxicology grading at the subsequent study visit (Appendix 4). Severe (≥ Grade 3) reactions will be recorded as AEs on day of vaccination.

Participants will utilize their eDiary to record reactogenicity following vaccination. All participants will record reactogenicity starting on the same day of the vaccinations and for a total of 7 days. Study site personnel will regularly review the eDiary for completeness. Should any reactogenicity event extend beyond 7 days after vaccination (toxicity Grade ≥ 1), then it will be recorded as an AE with a start date that matches Day 7 of the reactogenicity event and followed to resolution per FDA guidelines for AE capture. Following receipt of either dose of vaccine, reactogenicity events that meet the criteria for nasal swab for COVID-19 (eg, fever, generalized myalgia, etc.), and that occur after completion of Day 4 of reactogenicity reporting via the eDiary, should prompt the collection of a nasal swab and initiation of follow-up according to the directions for COVID-19 surveillance (Section 10.1). At any time after Day 0, severe COVID-19 should be reported as an SAE and managed as described in Section 10.1.3.

10.3.1.8 Pregnancy

A urine pregnancy test will be performed at screening and prior to each vaccination only for participants of childbearing potential. A positive urine pregnancy test at any time during the study will result in the participant not receiving any further vaccination and will initiate the prescribed follow-up for pregnancy outcome.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the trial vaccine may have interfered with the effectiveness of a contraceptive medication. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, preterm birth, normal birth or congenital abnormality) must be followed up and documented even after the participant has completed the study.

All reports of congenital abnormalities/birth defects/preterm (< 37 weeks gestation) are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as SAEs, but should be reported as a follow-up report for outcome of the pregnancy. All outcomes of pregnancy must be reported to ICON on a Pregnancy Outcomes Report Form.

Pregnancies must be reported to ICON Pharmacovigilance and Safety Services (PVSS) within 24 hours of awareness, using the reporting details provided in Section 10.3.6.

10.3.2 Time Period and Frequency for Collecting AE and SAE Information

All AEs reported or observed during the study will be recorded on the AE page of the eCRF.

Medical occurrences that begin prior to the first dose of trial vaccine will be recorded on the Medical History/Current Medical Conditions section of the eCRF not the AE section.

All unsolicited AEs of any severity will be collected from the time of first study vaccination through Day 49 (28 days after the second vaccination) (Table 1). Any relevant observations made prior to the first dose of trial vaccine are to be recorded on the AE eCRF but will not be considered TEAEs and will be reported separately from TEAEs.

MAAEs will be collected from the time of first study vaccination until Day 49, and MAAEs attributed to vaccine will be collected from the time of first study vaccination until completion of the EoS (Table 1).

All SAEs and AESIs will be collected from signing of informed consent until completion of the EoS (Table 1).

At any time after completion of the EoS visit, if an investigator learns of an SAE that could reasonably be considered related to trial vaccine, they should promptly notify the Sponsor.

10.3.3 Method of Detecting AEs, MAAEs and SAEs

Care will be taken not to introduce bias when detecting AEs, MAAEs and SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to enquire about AE occurrences. AESIs will be inquired about according to the specific diseases listed in Appendix 2.

10.3.4 Recording of AEs and SAEs

When an AE/SAE occurs, it is the responsibility of the investigator to review all available documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event. The investigator will then record all relevant AE/SAE information in the eCRF. For an SAE of severe COVID-19 (see Section 7.4), every effort should be made to obtain a nasal swab to be sent to the study central lab. This swab may be recorded in the Acute Illness Visit eCRF. Subjects with PCR-confirmed COVID-19 should subsequently be followed as per Section 10.1.2.

It is not acceptable for the investigator to send photocopies of the participant's medical records in lieu of completion of the AE/SAE eCRF page. There may be instances when copies of medical records for certain cases are requested. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission. The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

The following variables will be recorded for each AE: verbatim/AE description and date for AE start and stop, severity (refer to Section 10.3.4.1), seriousness (Section 10.3.1.3), causality (Section 10.3.4.2), whether the AE caused the participant to not receive the second dose of study vaccine (Section 10.3.4.3), any other action taken (Section 10.3.4.4), and the outcome (Section 10.3.4.5). A new AE must be recorded if the severity of the AE changes.

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

10.3.4.1 Assessment of Intensity (Severity)

The severity (or intensity) of an AE/SAE refers to the extent to which it affects the participant's daily activities and will be classified as mild, moderate, or severe using the following criteria:

- Mild (grade 1): These events require minimal or no treatment and do not interfere with the participant's daily activities.
- Moderate (grade 2): These events result in a low level of inconvenience or require minor therapeutic measures. Moderate events may cause some interference with normal functioning.

- Severe (grade 3): These events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

If the severity of an AE/SAE changes, the most intense severity should be reported. An AE/SAE characterized as intermittent does not require documentation of the onset and duration of each episode.

An event is defined as 'serious' when it meets at least one of the regulatory criteria listed in Section 10.3.1.3.

An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

10.3.4.2 Assessment of Causality

The investigator must assess the relationship between trial vaccine and each occurrence of each AE/SAE using their clinical judgement. A reasonable possibility of a causal relationship requires that there are facts, evidence, and/or biological plausibility to suggest a relationship, rather than that a relationship cannot be ruled out. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as a temporal relationship of the event to trial vaccine administration will be considered and investigated. The investigator will also consult the IB and/or Product Information (for marketed products) as part of their assessment.

For each AE/SAE, the investigator must document in the medical notes that they have reviewed the AE/SAE and have provided an assessment of causality. There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data. The investigator may change their opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment. The causality assessment is one of the criteria used when determining regulatory reporting requirements. If an SAE cannot be determined to be Not Causally Related to trial vaccine, it must be classified as Related.

Term	Definition
Not Related	There is no reasonable possibility of relationship to trial vaccine. The AE does not follow a reasonable temporal sequence from administration of trial vaccine or can be reasonably explained by the participant's clinical state or other factors (eg, concurrent diseases, and concomitant medications).
Related	There is a reasonable possibility of relationship to trial vaccine. The AE follows a reasonable temporal sequence from administration of trial vaccine and cannot be reasonably explained by the participant's clinical state or other factors (eg, concurrent diseases, or concomitant medications), represents a known reaction to trial vaccine or other vaccines in its class, is consistent with the known pharmacological properties of the trial vaccine, and/or resolves with discontinuation of the trial vaccine (and/or recurs with re-challenge, if applicable).

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

- Time relationship between trial vaccine injection and event's onset.
- Re-challenge following second vaccine.
- Medical history.
- Study treatment.
- Mechanism of action of trial vaccine.
- Class effect.
- Concomitant treatments in use.
- Withdrawal of study treatment.
- Lack of efficacy/worsening of existing condition.
- Possible vaccine enhancement of COVID-19.
- Erroneous treatment with study medication or concomitant medication.
- Protocol-related process.

10.3.4.3 Action Taken with Trial Vaccine Due to AE

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

- No action taken.
- Next dose delayed.
- Permanently discontinued/withdrawn from further study vaccination (with date).
- Not applicable.

10.3.4.4 Other Action Taken

Details of any other actions taken should be specified:

- Specific therapy/medication.
- Surgical or medical procedure.

- Prolonged hospitalization.

10.3.4.5 AE Outcome

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

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

10.3.5 Follow-up of AEs/SAEs

All AEs should be followed up until resolution, unless in the investigator's opinion, the AE is unlikely to resolve and has become a chronic underlying disease. SAEs, MAAEs or AESIs ongoing at the time of EoS should be reported according to Section 10.3.6.

10.3.6 Reporting of SAEs

All SAEs must be reported according to International Council for Harmonisation (ICH) GCP or local regulations, applying the regulation with the stricter requirements. Investigators and other study site personnel must inform appropriate ICON representatives of any SAE that occurs during the course of the study, from the time of informed consent until the EoS visit, regardless of whether it is judged to be causally related to trial vaccine or procedures. Notification must occur within 24 hours of when they become aware of it. The investigator should make every effort to obtain follow-up information on the outcome until the event is considered resolved, chronic and/or stable.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to ICON within 24 hours as described above. The date when the AE becomes serious should be notated in the eCRF or on the SAE form.

All SAEs will also be recorded in the eCRF. The investigator is responsible for informing the IEC/IRB of the SAE as per local requirements. Paper SAE forms should be completed at the study site and emailed within 24 hours of study site awareness of the event to the Central Receipt mailbox:

[redacted]

The report form should be attached to the email; a notification email of the event describing it in the email text is not sufficient. There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial SAE report. However, it is very important that the investigator always makes an assessment of causality for every event prior to transmission of the SAE report form.

Minimum criteria for a reportable event are:

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

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

10.3.6.1 Safety Reporting to Sponsor

ICON PVSS will forward the SAE and Pregnancy reports to the Sponsor's safety representative(s) within 1 business day or 3 calendar days (whichever is earlier) of becoming aware of it.

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

ICON will notify the Sponsor of any SAE and will perform follow-up activities with the concerned study site. Novavax will retain responsibility of expedited and periodic reporting to the US FDA and ICON for all other reporting according to national requirements Procedure and timelines for safety reporting are provided in the Safety Management Plan as agreed by ICON and the Sponsor. The investigator must comply with any applicable study site-specific requirements related to the reporting of SAEs (particularly deaths and SUSARs) to the IEC/IRB that approved the study. Investigators should provide written documentation of IEC/IRB notification for each report to the ICON PVSS. In accordance with ICH GCP, ICON PVSS will inform the investigators of findings that could adversely affect the safety of participant, impact the conduct of the study, or alter the IEC's/IRB's approval/favorable opinion to continue the study, as assessed by the Sponsor. In particular and in line with respective regulations, ICON PVSS will inform the investigators of SAEs. The investigator should place copies of Safety Reports in the Investigator Site File. National regulations with respect to Safety Report notifications to investigators will be taken into account. When specifically required by regulations and guidelines, the ICON PVSS will provide appropriate Safety Reports directly to the concerned lead IEC/IRB and will maintain records of these notifications. When direct reporting is not clearly defined by national or study site-specific regulations, the investigator will be responsible for promptly notifying the concerned IEC/IRB of any Safety Reports provided by the ICON PVSS and of filing copies of all related correspondence in the Investigator Site File.

10.3.6.3 24/7 Medical Emergency Coverage for Urgent Protocol-related Medical Questions

In a study-related health emergency, when assigned medical monitors for a study cannot be reached by a caller, for discussion of urgent medical-related questions an on-call physician can be reached 24/7 via an ICON Call-Center:

- Telephone: [redacted]

(Chargeable telephone number allowing global reach from both landlines and mobile phones)

- [redacted]

On this internet page, a list of country-specific toll-free telephone numbers is provided. It should be noted that not all countries globally have access to toll-free numbers as indicated on the "24/7 Medical Help-desk" index. Countries without toll-free numbers need to dial the chargeable number as indicated above. Furthermore, there may be restrictions when dialing toll-free numbers from a mobile phone.

10.3.7 Laboratory Assessments

Screening clinical laboratory tests will be performed at a designated laboratory. The following parameters will be collected:

Table 4 Clinical Laboratory Tests

Laboratory Testing Profile	Tests Included
Pregnancy testing	Only for participants of childbearing potential: • Urine pregnancy test at screening and prior to each vaccination

10.3.8 Physical Examination

Targeted physical examination, as indicated, will be performed at the visits specified in the SoA (Table 1).

Height and weight will be measured and BMI will be calculated at screening only, unless a participant's clinical condition changes such that reassessment of weight and BMI is medically indicated, which should then be recorded as part of an AE, as indicated below.

Examination at screening to include vital signs, height and weight (calculated BMI), and lymphatic assessment of upper extremities to allow for vaccination. Symptom-directed (targeted) physical examination will be performed at all other scheduled time points.

Any clinically significant changes from baseline should be recorded as AEs.

10.3.9 Vital Signs

Vital sign measurements will be recorded at screening and prior to vaccination on Days 0 and 21. Vital sign measurements, recorded as continuous variables, will include oral temperature (or via forehead/ear reader), respiratory rate and diastolic and systolic blood pressure (BP) (after participant is seated for at least 5 minutes). Pulse rate may be measured by pulse oximeter. Blood pressure should not exceed medically acceptable limits to ensure participants with uncontrolled hypertension are not included. Participants considered to have "white coat hypertension" should have a reduction in BP documented following a calming period. Body temperature should not exceed 38°C.

Vital sign measurements will be recorded as continuous variables prior to each vaccination. On vaccination days, vital sign measurements will be collected once before vaccination to ensure participant has controlled BP and heart rate and no evidence of fever prior to vaccination. If individual vital sign measurements are considered clinically significant by the investigator, vaccination may be withheld that day (or, as noted for BP, delayed briefly pending a calming period), and participants may return on a subsequent day for re-evaluation and vaccination, ideally, within the time window specified in the SoA (Table 1).

10.3.10 Overdose

A drug overdose is defined as the accidental or intentional use of a drug or medicine or an administration error in an amount that is higher than is normally used. Every overdose must be reported to ICON PVSS within 24 hours of awareness, using the details provided in Section 10.3.6 if the overdose was associated with an SAE. Other overdoses and those associated with non-serious AEs should be reported in the eCRF AE page. Only overdoses associated with a clinical SAE needs to be reported as an SAE. The quantity and duration of the excess dose should be documented in the eCRF.

Overdose in this study is specifically defined as any dose greater than the intended protocol dose (Section 9). In case of overdose, it is recommended that the participant be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment be administered immediately. Note that administration of the "wrong" vaccine is a protocol deviation, but not, in the absence of associated AE, an SAE.

10.4 Other Assessments

10.4.1 Medical and Social History

Medical and social history will capture prior and concomitant medical conditions, recent vaccinations (≤ 90 days), and significant surgical procedures. Living and working or school conditions will be recorded to assess possible high-risk environments.

10.4.2 Demographics

Demographic information will be collected at screening only and will include date of birth (day, month, and year), sex, race, ethnicity, weight, height, and BMI (derived).

10.4.3 eDiary

The eDiary is a validated data collection tool that generates an audit trail. Solicited AEs of reactogenicity, all subsequent AEs and COVID-19 symptomatology will be collected via participant reporting in the eDiary utilizing smartphone application(s). Participants who do not possess an appropriate device will be provided a device compatible with study requirements. All participants will be trained on the use of these applications at the initiation of the study, and a Help Desk will be available 24/7 for technical issues. For data entry issues, participants should contact the study site.

Study site personnel and central monitoring personnel will regularly review the eDiary for completeness.

Centralized monitoring of the electronic database will enable identification of any potential issues related to participant retention, including study participants who have missed regular reporting or non-compliant.

11 MEDICAL RESOURCE UTILIZATION

Healthcare requirements, utilization and medical assessments from participants who become ill on study will be defined in a separate substudy protocol.

12 STATISTICAL CONSIDERATIONS

12.1 Sample Size and Power

The sample size is driven by the total number of cases expected to achieve statistical significance for the primary efficacy endpoint; a total of up to approximately 30,000 participants ≥ 18 years of age will be enrolled to provide a target of 144 symptomatic COVID-19 illness PCR-confirmed SARS-CoV-2 infections. The estimated (through simulations) powers to reject the null hypothesis of VE lower bound of 95% CI ≤ 30% and achieving the point estimate of VE ≥ 50% simultaneously for the primary endpoint is summarized in Table 5.

Two formal interim analyses of efficacy and futility will be conducted based on the accumulation of approximately 50% and 75% of the total anticipated primary endpoints using O'Brien-Fleming boundary conditions. Power calculations were performed by 10,000 simulated trials that were created under various assumptions of VEs and analyzed using methods described in the "efficacy analysis" section without covariates. All simulations were performed in SAS V9.4.

Table 5 Power Under Various Vaccine Efficacy Assumptions

Assumed Vaccine Efficacy	Estimated Power			
Symptomatic COVID-19 Illness PCR-Confirmed SARS-CoV-2 Infection	Planned Interim Analyses		At Final Analysis	Overall (At Either Interim Analysis or Final Analysis)
	First (50%)	Second (75%)		
50%	**6.15%**	**19.26%**	**28.66%**	**54.07%**
55%	**13.72%**	**31.96%**	**30.32%**	**76.00%**
60%	**27.63%**	**40.50%**	**23.92%**	**92.05%**
65%	**47.84%**	**40.08%**	**10.67%**	**98.59%**
70%	**74.11%**	**23.47%**	**2.37%**	**99.95%**

A total of up to approximately 1,200 participants will be randomly selected for the immunogenicity assessment (IgG antibody to SARS-CoV-2 S protein, MN, and hACE2 inhibition) at Days 0 and 35. A random selection of 300 participants per country and age cohort will include approximately 200 vaccine and 100 placebo recipients.

Additional 2-stage random samplings are planned to facilitate the case-cohort sampling design for assessing immune correlates of risk and protection to be conducted in collaboration with external CoVPN and OWS statistical groups. The analytical approach including sampling plan details will be documented in a separate SAP to be developed prior to the unblinding by the external statistics groups.

12.2 Analysis Sets

The following analysis sets are identified for analysis.

12.2.1 Intent-to-Treat (ITT) Analysis Set

The ITT analysis set will include all participants who are randomized, regardless of protocol violations or missing data. The ITT analysis set will be used for participant disposition summaries and will be analyzed according to the treatment arm in which the participant was randomized.

12.2.2 Full Analysis Set (FAS)

The FAS will include all participants who are randomized and received at least 1 dose of study vaccine/placebo, regardless of protocol violations or missing data. The FAS population will be analyzed according to the treatment group to which they were randomized. The FAS analysis sets will be used for supportive analyses.

12.2.3 Safety Analysis Set

The safety analysis set will include all participants who receive at least 1 dose of trial vaccine. Participants in the safety analysis set will be analyzed according to the vaccine actually received. In cases where information is available that indicates that a participant received both active and placebo, the participant will be analyzed as part of the active group.

12.2.4 Per-Protocol Efficacy (PP-EFF) Analysis Set

The PP-EFF analysis set will include all participants who receive the full prescribed regimen of trial vaccine and have no major protocol deviations that occur before the first COVID-19 positive episode and are determined to affect the efficacy outcomes, including baseline SARS-CoV-2 seropositivity. Although the study will enroll participants regardless of SARS-CoV-2 serologic status at the time of vaccination, any participants with confirmed infection or prior infection due to SARS-CoV-2 at baseline, by nasal swab PCR or serology, will be excluded from the PP-EFF population. PP-EFF will be the primary set for all efficacy endpoints.

The PP-IMM analysis set will be determined for each study visit. The PP-IMM analysis set will include participants that have at least a baseline and 1 serum sample result available after vaccination and have no major protocol violations that are considered clinically relevant to impact immune response at the corresponding study visit, including nasal PCR-positive swabs or seropositivity for SARS-CoV-2 prior to the visit in question. For participant visits on or after Day 21, participants must receive the second vaccination to be included in the PP-IMM analysis set. Prior exposed participants will be determined using baseline SARS-CoV-2 nasal swab or seropositivity at screening to assess if immune responses differ between previously exposed and unexposed individuals.

The review and determination for exclusion from the PP analysis set will be carried out in a blinded fashion by a study clinician prior to unblinding for the interim analysis based on all available information from the locked database.

12.2.5 Participant Disposition

A CONSORT diagram and table displays will be generated to present the number of participants screened, the number enrolled and eligible for vaccination, the number randomized to each trial vaccine arm, the number receiving the first and second vaccination, the number of early terminations, the number completing the study, and the number eligible for analysis. Displays of participants included and excluded from each analysis population along with the reason for exclusion will be provided by trial vaccine arm. A review of participant disposition will also be summarized by age strata, race, ethnicity, sex at birth, and country.

12.3 Statistical Analyses

The SAP will include a more technical and detailed description of the statistical analyses. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints. Primary and secondary efficacy and safety endpoints will be evaluated by key demographic characteristics, such as age strata, race, ethnicity, sex at birth, and country.

12.3.1 Primary Endpoint

The primary endpoint will be analyzed on the PP-EFF analysis set and supported by analysis of the FAS.

The VE is defined as VE (%) = (1 – RR) x 100, where RR = relative risk of incidence rates between the 2 trial vaccine groups (SARS-CoV-2 rS / Placebo). The RR will be estimated by exponentiating the treatment group coefficient from a Poisson regression analysis with robust error variance [Zou 2004]. The age strata will be included in the model as a covariate. To assess incidence rates rather than absolute counts of cases, accounting for differences in follow-up times starting with 7 days after the second vaccination among participants, an offset will be utilized in the Poisson regression. A two-sided, alpha level adjusted confidence interval (CI) will be constructed around the estimate.

A super superiority of the vaccine efficacy at each analysis will be used to determine success of the primary endpoint. An alpha level adjusted hypothesis test will be conducted with the following hypotheses:

H_0: VE $\leq$ 0.30 (RR $\geq$ 0.70)

H_1: VE > 0.30 (RR < 0.70)

Rejection of the null hypothesis demonstrates a statistically significant VE with a lower bound of CI > 30%. In order to be considered for emergency use authorization or licensure by the FDA, a

vaccine must show super superiority where there is a minimum VE of 50% and a lower bound of two-sided alpha adjusted confidence bound of at least 30%. Based upon the number of primary efficacy endpoints planned for analysis, a lower bound of more than 30% corresponds with a VE point estimate of at least 50%.

12.3.2 Secondary Endpoints

The key secondary efficacy endpoint and other secondary efficacy endpoints will be analyzed using the same manner as the primary efficacy analysis described in protocol Section 12.3.1. The analysis of the key secondary endpoint will be carried out using a one-sided alpha of 0.025 only after the successful demonstration the primary endpoint to preserve the Type I error rate. All remaining secondary efficacy endpoints will also be performed using an unadjusted one-sided 0.025 alpha level.

The secondary immunogenicity analyses will be performed using the PP-IMM analysis set and FAS.

For the serum antibody levels specific for the SARS-CoV-2 S protein antigen(s) (IgG antibody to SARS-CoV-2 S protein and hACE2 inhibition) and MN, the geometric mean at each study visit, the geometric mean fold rise (GMFR) comparing to the baseline (Day 0) at each post-vaccination study visit, and the GMFR comparing pre- and post-second dose, along with 95% CI will be summarized by trial vaccine group. The 95% CI will be calculated based on the t distribution of the log-transformed values for geometric means or GMFR, then back transformed to the original scale for presentation.

Similar summaries will be generated for the other immunogenicity endpoints and other assays if conducted.

12.3.3 Statistical Models

The RR and its CI will be estimated using Poisson regression with robust error variance [Zou 2004]. The generalized linear model with unstructured correlation matrix (robust error variances) will be used. The explanatory variables in the model will include the trial vaccine group. The dependent variable will be the incidence rate of the endpoint of interest. The robust error variances will be estimated using repeated statement and the participant identifier. The age strata will be included in the model as a covariate. To account for the censoring in the analysis, the offset will be defined as the natural log of the time from the start of follow-up (7 days post second vaccination) to the outcome of interest or to the end of study. Poisson distribution will be used with a logarithmic link function. The following is a sample of SAS code used to estimate the RR:

```
proc genmod data = <DATASET>;
      class armcd usubjid agestrata;
      model <OUTCOME> = armcd agestrata / dist = poisson link = log
      offset=<LN(TIMEVAR)>;
      repeated subject = usubjid/ type = unstr;
      estimate 'Beta' <OUTCOME> 1 -1/ exp;
run;
```

A Cox proportional hazards model with the age strata as a covariate will also be developed as a supportive analysis to the Poisson regression. The model will follow the same explanatory and dependent variables as the Poisson model and will censor participants based on their follow-up time available.

12.3.4 Handling of Missing Data

No imputation of missing primary or secondary endpoints will be *a priori,* to define the success of this study. All data recorded on the eCRF will be included in data listings and included in the clinical study report.

To assess the impact of missing values on the primary conclusions of this study, a tipping point analysis method will be conducted. The missing endpoint results in the control group will be imputed as non-endpoint, while participants in the active trial vaccine group with missing endpoint results will be imputed as an endpoint. If the primary endpoint is found to be significant, it will be assumed that the missing data has no impact on the conclusions of the study. If the primary endpoint is no longer significant a grid will be constructed of all possible (*mv +1*) by (*mp+1*) imputed outcomes for missing values by assigning imputed number of "endpoints" from 0 to the number in the vaccine group (mv) and 0 to the number in the placebo group (mp). For each possible imputed outcome, the overall VE and the corresponding CI will be constructed using the same statistical method used for the primary endpoint. The imputed data points in the grid will be evaluated against the H0: VE $\leq$ 30%. This grid will allow for an assessment of the impact of missing data on the primary conclusions of the trial.

Any further imputations required for reporting of AEs, medical history, and medications will be defined in the SAP.

12.3.5 Safety Analyses

Accumulating safety data, blinded to treatment group, will be reviewed weekly by the PSRT to detect possible signals of a concerning frequency or severity of solicited or unsolicited AEs that may require escalation to the DSMB for unblinded review.

In formal analyses, numbers and percentages (with 95% CIs based on the Clopper-Pearson method) of participants with solicited local and systemic AEs through 7 days after each vaccination will be summarized by trial vaccine group and the maximum toxicity grade over 7 days after each vaccination. The duration of solicited local and systemic AEs after each vaccination will also be summarized by trial vaccine group.

Unsolicited AEs will be coded by preferred term and system organ class using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by trial vaccine group as well as by severity and relationship to trial vaccine. AEs through 28 days after second vaccination; all MAAEs related to vaccine, SAE, or AESI through EoS will be listed separately and summarized by trial vaccine group.

Vital sign measurements will be summarized by trial vaccine group at each time point using descriptive statistics.

Concomitant medications will be summarized by trial vaccine group and preferred drug name as coded using the WHO drug dictionary.

12.4 Interim Analysis

Two formal interim analyses of efficacy and futility for review by the independent DSMB, as described in the DSMB Charter, will be conducted based on the accumulation of approximately 50% and 75% of the total anticipated primary endpoints. For these analyses, database freeze for analysis of the primary efficacy and selected secondary endpoints (eg, disease severity, key safety and Day 35 immunogenicity endpoints) will be performed to monitor the benefit-risk profile of vaccination in the 2 age strata. The interim analyses will be performed by an unblinded Biostatistics and Programming team and reviewed by the independent DSMB that will make recommendations with regard to the continuation of the trial. Any early stopping for efficacy will be based on the PP-EFF analysis set only. Regardless of the outcomes at either interim analysis or the final analysis, the study will remain blinded at the participant level for study site personnel and study participants until the end of the study (24 months after the first vaccination) while the Sponsor will be unblinded at the participant level to prepare for regulatory submissions. There will be an unblinded statistician and programmer isolated (by firewall) from study personnel. They will complete these analyses independent of the study team and Sponsor. A separate Statistical Monitoring Plan will include a detailed description of the responsibilities of the ICON unblinded statistician and the communication plan with the DSMB.

The interim analyses will follow standard group-sequential design using the O'Brien-Fleming boundary conditions. The nominal alpha to be spent for the final analysis will be recalculated using the Lan-DeMets alpha spending function based on the actual numbers of events used for the interim analyses and the numbers of endpoints to be used for the final analysis.

Table 6 summarizes the timing, number of endpoints and statistical success boundaries at the formal interim analyses and the final analysis.

Table 6 Interim and Final Boundaries Using O'Brien-Fleming Spending Function

Information Fraction (% of total endpoints)	Blinded Total Number of Endpoints	Nominal Alpha	VE Boundary for Lower Bound Confidence Interval > 30%
First interim analysis at 50%	72	0.00153	~66%
Second interim analysis at 75%	108	0.00916	~57%
Final analysis at 100%	144	0.02200	~50%

Calculated using PROC SEQDESIGN procedure in SAS (Version 9.4)

```
proc seqdesign errspend
        plots=(asn power errspend) boundaryscale=pvalue;
        OneSidedOBrienFleming: design nstages=3
                                        method(alpha)=errfuncobf
                                        alt=upper stop=reject
                                        alpha=.025
                                        info=cum(0.5 0.75 1);
run;
```

In addition, a futility analysis will be performed using the same data set (PP-EFF). The futility analysis will be based on the two-sided 95% CIs for the primary and key secondary efficacy endpoints based on the PP-EFF analysis set. The futility assessment will be carried out for the 2 endpoints based on the upper bound of two-sided 95% CIs (UBCI) without a multiplicity adjustment:

1. UBCI for the primary efficacy endpoint (symptomatic COVID-19) < 50%
2. UBCI for the key secondary efficacy endpoint (moderate/severe COVID-19) < 50%

If both futility criteria are met, the independent DSMB will make recommendations with regard to the discontinuation of the trial, with regard to continued vaccinations and/or blinded follow up of trial participants.

12.5 Monitoring Potential Vaccine Harm

The DSMB will monitor the study for potential vaccine harm based on imbalance in the primary efficacy endpoint, ie, all mild, moderate or severe COVID-19 cases, and severe COVID-19 cases between SARS-CoV-2 rS with Matrix-M1 adjuvant versus placebo. In order to facilitate the timely identification of the severe COVID-19 cases, the cases will be ascertained through both the efficacy surveillance and the SAE reporting. Monitoring for vaccine harm will be based on the Safety Analysis Set, defined as all randomized participants who received at least 1 dose of study vaccination. Participants will be analyzed according to the study vaccination they actually received regardless of the group to which they were randomized. For harm monitoring, cases will be counted starting on Day 0 after the first dose of study vaccination. For mild, moderate or severe COVID-19, only cases where the onset of symptoms is on Day 4 or later will be included.

Monitoring for harm will be performed at identification of each analysis-ready COVID-19 case once the 8th COVID-19 case has occurred, or the 8th severe COVID-19 case at any time post first vaccination (whichever is identified earlier). The 8th case was chosen because that is the minimum number of total cases required to reach the harm monitoring boundary if all 8 cases occur in the vaccine group.

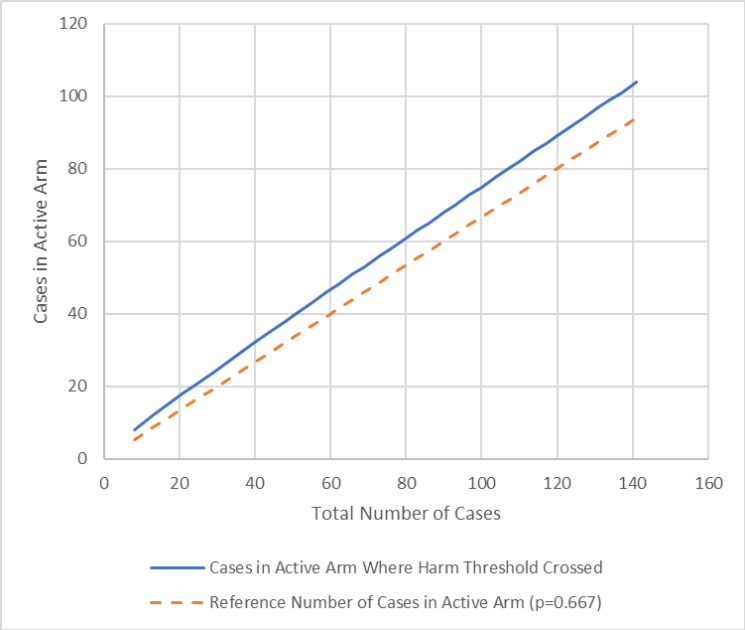
The ICON unblinded statistician will continuously monitor the trial (ie, examine the data after each mild, moderate and severe COVID-19 case and each severe COVID-19 case, respectively) for early evidence of a potential elevated rate of mild, moderate and severe COVID-19 or severe COVID-19 in the SARS-CoV-2 rS with Matrix-M1 adjuvant group compared to the placebo group, in the Safety Analysis Set. The DSMB chair will be notified on a weekly basis as to the status of the number of cases observed and if the boundary conditions have been crossed. If the prespecified stopping boundary is reached for either mild, moderate and severe COVID-19 or severe COVID-19, then the ICON unblinded statistician will immediately inform the DSMB that the harm rules have been met. This monitoring guideline is chosen to allow stopping for prudence as early as possible, maximizing participant safety. In addition, IRBs/IECs will be notified if halting criteria are met and of any decisions made by the DSMB.

Potential vaccine harm is continuously monitored by evaluating number of mild, moderate and severe COVID-19 and severe COVID-19 cases separately, in the vaccine and placebo arms. The monitoring for each is implemented with exact one-sided binomial tests of H0: $p \leq 2/3$ versus H1: $p > 2/3$ (ie, H0: RR ≤ 1.0 versus H1: RR > 1.0, where RR is relative risk of the rate in the SARS-CoV-2 rS with Matrix-M1 adjuvant group over the rate in the placebo group), where p is the probability that a case participant would be in the SARS-CoV-2 rS with Matrix-M1 adjuvant group given the total number of cases. The bounds for harm monitoring are based on the assumption that VE = 0% (corresponds to $p = 2/3$ or 0.67). The actual ratio, p, between the 2 treatment groups will be re-established once the final number of participants for the Safety Analysis Set have been determined.

For mild, moderate or severe COVID-19, each test is performed at one-sided type I error rate of 0.05. At the interim analysis, both efficacy and non-efficacy will be evaluated. After the interim analysis, the DSMB can decide whether to continue to monitor using the harm bound provided up to 144 primary endpoint cases.

For severe COVID-19, monitoring of severe COVID-19 cases will be performed using a similar approach as that for COVID-19, to allow early stopping if there is evidence of an elevated rate of severe disease in the vaccine versus placebo group. The monitoring for potential harm based on the number of severe COVID-19 cases will also continue at least until the first interim analysis. Figure 1 presents example stopping boundaries based on the planned randomization ratio of 2:1 (see Appendix 3 for detailed list of example boundaries).

Figure 1 Example of Stopping Boundaries for Potential Vaccine Harm



Stopping bounds for potential vaccine harm are based on exact binomial test conditional on the total number of cases, each test to be performed at one-sided alpha of 0.05.

12.6 Safety Monitoring

This protocol has extensive safety monitoring in place. Safety is monitored daily by the ICON Medical Monitor, Novavax Pharmacovigilance and Safety Surveillance Physicians, and routinely by the 2019nCoV-301 PSRT. In addition, an independent DSMB periodically reviews study data, including unblinded study data if/when needed.

The 2019nCoV-301 PSRT is composed of the following members: medical and statistical representatives from the Sponsor, ICON and CoVPN network, as outlined in the PSRT Charter.

- Novavax study responsible Safety Physician
- Novavax Global Medical Lead, Clinical Development
- DAIDS medical officer representative
- Protocol chair and co-chairs
- BARDA Clinical Team Physician
- CoVPN Protocol Team Lead
- OWS Protocol Team Lead
- ICON Medical Monitor

The clinician members of the 2019nCoV-301 PSRT are responsible for decisions related to participant safety, as outlined in the PSRT Charter.

The Protocol Team clinic coordinator, clinical data manager, vaccine developer representative, clinical trial manager, and others may also be included in the 2019nCoV-301 PSRT meetings.

12.7 Data Safety and Monitoring Board

A centralized DSMB will be established in collaboration with NIH, NIAID, BARDA and Novavax according to the charter dictated by the participating groups. This group will then review interim unblinded data on a monthly basis and make recommendations with respect to safety and emerging efficacy.

The NIAID DSMB assesses the effects of the study vaccine during the trial, provides other monitoring as described in Section 12.4, and may give advice to the 2019nCoV-301 Protocol Team leadership, the Oversight Group, and PSRT. More details on the role of and the data provided to the DSMB will be described in a DSMB Charter and SAP.

The DSMB will periodically review accumulating unblinded safety data by group. Prior to each meeting, the ICON unblinded statistician will provide the DSMB with data as described in SAP. Reports will be cumulative, generated from an up-to-date data file. Based on the reports, the DSMB will determine whether to recommend that the study should be continued, modified, or stopped, including for safety reasons.

The DSMB may recommend any steps to ensure the safety of study participants and the integrity of the trial. Furthermore, the DSMB may recommend that the trial be terminated or that specific groups be withdrawn from the study, if any subgroup manifests serious or widespread side effects. To guarantee the unrestricted performance of its task, the DSMB may receive the individual study morbidity and mortality data from the ICON unblinded statistician.

The DSMB will be informed immediately by the ICON unblinded statistician if the pre-specified stopping boundary is met, indicating that the vaccine causes harm by increasing the rate of mild, moderate or severe COVID-19. In addition, the DSMB will monitor the study for high vaccine efficacy or for futility to detect vaccine activity.

13 ETHICS

13.1 Independent Ethics Committee/Institutional Review Board

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

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

13.2 Documentation of Informed Consent

The nature and purpose of the study shall be fully explained to each participant (or their legally responsible guardian). They must be informed that participation is voluntary.

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

Participants will be requested to provide the name and contact information for an emergency contact and to provide consent for serum banking for future testing to support establishment of correlates of protection against SARS-CoV-2 infection and disease.

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

14 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Conduct of the Study

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

This study shall be conducted in accordance with the provisions of the Declaration of Helsinki (October 2013), FDA (US Title 21 CFR, Part 312, Sections 312.50 and 312.56), European Union (EU) (536/2014) and with ICH GCP (CPMP/ICH/135/95).

The investigator will be responsible for the following:

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

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

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

14.2 Site Monitoring

The monitoring strategy for the study foresees a risk-based monitoring approach, in line with the relevant FDA and EMA recommendations, and will be described in detail by the study-specific risk-based Monitoring Plan.

Study site monitoring includes both source data review and source data verification. Study site monitors perform source data review of critical procedures to ensure that the safety and rights of participants are being protected and that the study is being conducted in accordance with the currently approved protocol, any other study agreements, ICH GCP, and all applicable regulatory requirements. Study site monitors perform source data verification of critical data to confirm transcription of data entered into the eCRF by authorized study site personnel are accurate, complete, and verifiable from source documents.

Monitoring details describing strategy (eg, risk-based initiatives in operations/quality such as Risk Management, Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

The investigator, as part of his/her responsibilities, is expected to co-operate with ICON in ensuring that the study adheres to GCP requirements. The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF. The investigator may not recruit participants into the study until such time that a visit, or with the agreement of the Sponsor, attendance at the investigator meeting (or equivalent training), has been made by a Sponsor/ICON monitor to conduct a detailed review of the protocol, source documents and eCRF.

The investigator shall grant direct access of original source documents and study records to the ICON Site Monitor in order to conduct source data review, to ensure that the participants' well-being is maintained, data are being recorded in an adequate manner according to ALCOAC principles (ie, that they are attributable, legible, contemporaneous, original, accurate, and complete), that protocol and GCP adherence is satisfactory, and to verify accurate transcription of data to the eCRF.

15 DATA HANDLING AND RECORD KEEPING

15.1 Case Report Forms/Source Data Handling

All required study data must be entered by study site personnel in the eCRF or by study participants in the eDiary created for the study. These data collection tools are a validated EDC system that contains a system generated audit trail. Data required according to this protocol are recorded by study site personnel via data entry into the internet-based EDC software system or by study participant via the eDiary on their personal electronic device (smartphone). The investigator shall ensure that all data from participant visits are promptly entered into the eCRFs in accordance with the specific instructions given. The investigator must sign each eCRF to verify the integrity of the data recorded. All internal ICON and external study site personnel seeking access to the eCRF are supported by a Service Desk (if applicable). At the end of the study all data captured electronically will be provided to the investigator on CD ROM for archiving at the study site.

The investigator must maintain source documents, such as laboratory reports, consultation reports, and complete medical history and physical examination reports. All information in the eCRF must be traceable to the participant's source documents.

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

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

15.2 Data Protection

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred. The participant must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant. The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

15.3 Dissemination of Clinical Study Data

Regardless of whether the study is completed or prematurely terminated, the Sponsor will ensure that clinical study reports are prepared and provided to regulatory agency(ies) as required by the applicable regulatory requirement(s). The Sponsor will also ensure that clinical study reports in marketing applications meet the standards of the ICH E3: Structure and Content of Clinical Study Reports. Where required by applicable regulatory requirements, an investigator signatory

will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review complete study results.

15.4 Retention of Essential Documents

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

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the trial vaccine or per local regulation, whichever is longer. These documents should be retained for a longer period, however, if required by applicable regulatory requirements or by an agreement with the Sponsor. It is the Sponsor's responsibility to inform the investigator/institution as to when these documents are no longer need to be retained.

16 FINANCING AND INSURANCE

The investigator is required to provide financial disclosure information to allow the Sponsor to submit the complete and accurate certification or disclosure statements required under US Title 21 CFR Part 54 and local regulations. In addition, the investigator must provide to the Sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study. Neither the Sponsor nor designee nor the study site is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the Sponsor nor designee nor the study site is financially responsible for further treatment of the disease under study.

17 PUBLICATION POLICY

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

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

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

18 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this study will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the study. The study leadership in conjunction with the Sponsor has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

19 SIGNATURE OF INVESTIGATOR

PROTOCOL TITLE: A Phase 3, Randomized, Observer-Blinded, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Immunogenicity of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine (SARS-CoV-2 rS) with Matrix-M1™ Adjuvant in Adult Participants ≥ 18 Years

PROTOCOL NUMBER: 2019nCoV-301

I agree to conduct Protocol 2019nCoV-301 in accordance with the terms and conditions of the protocol, ICH guidelines on GCP and with applicable regulatory requirements. All information pertaining to the study shall be treated in a confidential manner.

((Type name and job title))	Date (day/month/year)

20 REFERENCE LIST

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21 APPENDICES

Appendix 1: Protocol Change History

Protocol Version 3.0, 16 November 2020 (revised from Version 2.0, 02 October 2020)

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

Location of Change	Change/Modification in Version 3.0
Section 2 (Primary Endpoint); Section 7.4	• Clarified the primary endpoint by deleting "with each symptom reported for at least 2 consecutive days."
Section 2 (Key Secondary Endpoint); Section 7.5.1	• Clarified the key secondary endpoint by deleting "with each symptom reported for at least 2 consecutive days."
Section 2 (Other Secondary Endpoint); Section 7.5.2	• Clarified the first other secondary endpoint by deleting "that is reported for at least 2 consecutive days."
Section 2 (Synopsis - Study Design)	• Added that the procedure for maintaining the blind for all vaccinations is described in the Pharmacy Manual for clarity. • Clarified that unblinded study site personnel who manage unblinded product can administer the product if qualified to do so. • Clarified that the initiation of the study was Day 0. • Corrected the number of participants in the Immunogenicity Population to 1,200. • Clarified that participants will be provided with an oral thermometer on Day 0 and instructed to monitor body temperature throughout the first 12 months of the study. • Clarified that starting on Day 4, through the first 12 months of the study, suspected symptoms of COVID-19 are to be reported in the eDiary. • Added that medically attended swabs collected at the Unscheduled Acute Illness Visit will be processed according to procedures described in the Laboratory Manual for clarity. • Added definition of mild exercise for participants measuring oxygen saturation for clarity. • Clarified that PCR-positive nasal swabs are to be confirmed at the central laboratory. • Clarified that an Unscheduled General Visit may be conducted by study personnel in the event of a general medical issue other than COVID-19 symptomatology. • Clarified that for participants who terminate the study early, an EoS telephone visit will occur to collect maximum safety data and blood sample, if possible.
Section 2 (Number of Participants and Statistical Methods and Sample Size Calculations)	• Clarified that up to approximately 30,000 participants were to be enrolled in the study.
Section 2 (Synopsis - Exclusion Criteria); Section 8.3.2	• Revised Exclusion Criterion 1b to define undetectable HIV RNA as RNA < 50 copies/mL for clarity. • Clarified that the criteria for meeting Exclusion Criterion 5 is judged to cause significant immunocompromise. • Clarified that the criteria for meeting Exclusion Criterion 8 is chemotherapy judged to cause significant immunocompromise.

Location of Change	Change/Modification in Version 3.0
Section 2 (Synopsis - Reference Therapy, Dose and Duration of Administration)	• Added the injection volume (0.5 mL) of normal saline (placebo) for clarity.
Section 2 (Synopsis - Statistical Methods and Sample Size Calculations)	• Revised wording of analysis sets to clarify that the PP analysis sets for efficacy and immunogenicity were the primary analysis sets of the study, the ITT analysis set was for participant disposition, and the FAS was for supportive analyses. • Clarified that participants receiving both vaccine and placebo would be analyzed as part of the vaccine group. • Separated the PP-EFF and PP-IMM definitions for clarity and provided for context to the PP-IMM definition for consistency with the protocol. • Added that the review and determination for exclusion from the PP analysis set will be carried out in a blinded fashion by a study clinician prior to unblinding for the interim analysis based on all available information from the locked database.
Section 2 (Synopsis – Primary Endpoint); Section 12.3.1	• Removed country as a covariate based on comments received from the FDA. • Added the definition of VE per FDA guidance.
Section 2 (Synopsis – Secondary Endpoint)	• Changed the alpha for the key secondary endpoint from two-sided alpha of 0.05 to one-sided alpha of 0.025 per FDA comments. • Added that secondary immunogenicity analyses will also be performed using the FAS.
Section 2 (Synopsis – Interim Analyses)	• Added that the nominal alpha to be spent for the final analysis will be recalculated using the Lan-DeMets alpha spending function based on the actual numbers of events used for the interim analyses and the numbers of endpoints to be used for the final analysis. • Removed language regarding additional interim analyses requested by the DSMB.
Section 2 (Synopsis - Monitoring Potential Vaccine Harm); Section 12.5	• Clarified language pertaining to harm monitoring starting on Day 0 for consistency across the protocol.
Section 2 (Data and Safety Monitoring Board); Section 12.7	• Added mild to rate of moderate or severe COVID-19 for consistency across the protocol.
Section 3 (Schedule of Assessments)	• Added assessment of vital signs at the Screening visit for consistency across the protocol. • Clarified that starting on Day 4, through the first 12 months of the study, suspected symptoms of COVID-19 are to be reported in the eDiary. • Added cross-references to Appendix 2 for AESIs for clarity.
Section 5 (List of Abbreviations)	• The list of abbreviations was updated based on changes made to the synopsis/body of the protocol.
Section 6.5 (Rationale for Dose Selection)	• Clarified that unblinded study site personnel who manage unblinded product can administer the product if qualified to do so.

Location of Change	Change/Modification in Version 3.0
Section 8.1 (Study Design Description)	• Clarified that up to approximately 30,000 participants (up to 20,000 in the SARS-CoV-2 rS with Matrix-M1 adjuvant group and up to 10,000 in the placebo group). • Added that the procedure for maintaining the blind for all vaccinations is described in the Pharmacy Manual for clarity. • Clarified that unblinded study site personnel who manage unblinded product can administer the product if qualified to do so. • Clarified that the initiation of the study was Day 0. • Corrected the number of participants in the Immunogenicity Population to 1,200. • Clarified that participants will be provided with an oral thermometer on Day 0 and instructed to monitor body temperature throughout the first 12 months of the study. • Clarified that starting on Day 4, through the first 12 months of the study, suspected symptoms of COVID-19 are to be reported in the eDiary. • Added definition of mild exercise for participants measuring oxygen saturation for clarity. • Clarified that PCR-positive nasal swabs are to be confirmed at the central laboratory. • Clarified that an Unscheduled General Visit may be conducted by study personnel in the event of a general medical issue other than COVID-19 symptomatology. • Clarified that for participants who terminate the study early, an EoS telephone visit will occur to collect maximum safety data and blood sample, if possible. • Added mild to rate of moderate or severe COVID-19 for consistency across the protocol.
Section 8.2 (Discussion of Study Design)	• Clarified that up to approximately 30,000 participants were to be enrolled in the study.
Section 8.8.1 (Trial Vaccine Discontinuation)	• Added that participants who discontinue due to an AE should be followed to resolution of the AE or determination that it is a chronic condition.
Section 8.8.2 (Study Temporary Discontinuation/Vaccine Pause)	• Added cross-reference to section on vaccine-enhanced disease for clarity.
Section 9.1 [Administration of Study Treatment(s)]; Section 9.5 [Blinding and Randomization of Study Treatment(s)]	• Clarified that unblinded study site personnel who manage unblinded product can administer the product if qualified to do so.
Section 9.2.1 (Packaging and Labelling)	• Clarified that 0.9% sodium chloride for injection will be used for placebo.
Section 9.4 (Prior Vaccinations and Concomitant Therapy)	• Clarified that non-study medications, therapies, or vaccines will be recorded in the eCRF.
Section 9.6 (Procedure for Breaking the Randomization Code)	• Added that the IWRS will also notify the PSRT that the randomization code has been broken.
Section 9.7 (Study Treatment Accountability)	• Added that all used and unused trial vaccines will be reconciled and retained or destroyed according to applicable regulations for consistency with the Pharmacy Manual.

Location of Change	Change/Modification in Version 3.0
Section 10.1.1 (Active Surveillance for COVID-19)	• Added that symptoms of severe COVID-19 should be reported as an SAE (important medical event) beginning on Day 0 following the first study vaccine administration and appropriate medical care should be sought. • Clarified that starting on Day 4, through the first 12 months of the study, suspected symptoms of COVID-19 are to be reported in the eDiary.
Section 10.1.2 (Unscheduled Acute Illness and Convalescent Visits)	• Added that medically attended swabs collected at the Unscheduled Acute Illness Visit will be processed according to procedures described in the Laboratory Manual for clarity. • Clarified that PCR-positive nasal swabs are to be confirmed at the central laboratory.
Section 10.1.3 (Nasal Swabs for Virus Detection)	• Added that participants who experience an SAE of severe COVID-19 any time after Day 0 should, if at all possible, have a nasal swab obtained (by site personnel or other healthcare personnel) to be sent by the study site to the study central laboratory. Such a swab, if obtained, will constitute the medically attended nasal swab recorded on the Acute Illness Visit form. • Clarified that starting on Day 4, through the first 12 months of the study, suspected symptoms of COVID-19 are to be reported in the eDiary. • Clarified that participants will be instructed on the procedure for arranging transport of swabs to the central lab.
Section 10.1.4 (FLU-PRO)	• Clarified that starting on Day 4, through the first 12 months of the study, suspected symptoms of COVID-19 are to be reported in the eDiary. •
Section 10.1.5 (Oxygen Saturation Monitoring)	• Added definition of mild exercise for participants measuring oxygen saturation for clarity. •
Section 10.2 (Immunogenicity Assessments)	• Corrected the number of participants in the Immunogenicity Population to 1,200.
Section 10.3 (Safety Assessments); Section 10.3.1.5 (Adverse Event of Special Interest)	• Clarified that AESIs specific to complications of potential disease enhancement for COVID-19 will also be monitored.
Section 10.3.1.3 (Serious Adverse Events)	• Added that events of severe COVID-19 constitute important medical events for this study.
Section 10.3.1.7 (Reactogenicity Symptoms)	• Clarified that reactogenicity events extending beyond 7 days after vaccination will be recorded as an AE with a start date that matches Day 7. • Added that at any time after Day 0, severe COVID-19 should be reported as an SAE and managed accordingly.
Section 10.3.4 (Recording of AEs and SAEs)	Added that participants who experience an SAE of severe COVID-19 any time after Day 0 should, if at all possible, have a nasal swab obtained (by site personnel or other healthcare personnel) to be sent by the study site to the study central laboratory. Such a swab, if obtained, will constitute the medically attended nasal swab recorded on the Acute Illness Visit form.
Section 10.3.9 (Vital Signs)	• Added that blood pressure should not exceed medically acceptable limits to ensure participants with uncontrolled hypertension are not included for clarity. • Added that participants considered to have "white coat hypertension" should have a reduction of in blood pressure documented following a calming period.

Location of Change	Change/Modification in Version 3.0
Section 10.4.1 (Medical and Social History)	• Added that living and working or school conditions will be recorded to assess possible high-risk environments.
Section 10.4.3 (eDiary)	• Clarified that study site personnel and central monitoring personnel will regularly review the eDiary for completeness.
Section 12.1 (Sample Size and Power)	• Clarified that up to approximately 30,000 participants were to be enrolled in the study. • Corrected the number of participants in the Immunogenicity Population to 1,200, including the breakdown of randomly selected participants per country and age cohort. • Deleted the immunogenicity sample size assumptions. • Deleted the specifics of the random selection of participant for the additional 2-stage random samplings to assess immunogenicity.
Section 12.2 (Analysis Sets)	• Revised wording of analysis sets to clarify that the PP analysis sets for efficacy and immunogenicity were the primary analysis sets of the study, the ITT analysis set was for participant disposition, and the FAS was for supportive analyses. • Clarified that participants receiving both vaccine and placebo would be analyzed as part of the vaccine group. • Separated the PP-EFF and PP-IMM definitions for clarity and clarified the PP-IMM definition.
Section 12.3.2 (Secondary Endpoints)	• Changed the alpha for the key secondary endpoint from two-sided alpha of 0.05 to one-sided alpha of 0.025 per FDA comments. • Added that secondary immunogenicity analyses will also be performed using the FAS. • Deleted the analysis of covariance model for non-randomized comparisons of subgroups for the immunogenicity analysis.
Section 12.3.3 (Statistical Models)	• Removed country as a covariate based on comments received from the FDA.
Section 12.4 (Interim Analysis)	• Added that the nominal alpha to be spent for the final analysis will be recalculated using the Lan-DeMets alpha spending function based on the actual numbers of events used for the interim analyses and the numbers of endpoints to be used for the final analysis. • Corrected the nominal alpha for the second interim analysis at 75% to 0.00916. • Corrected the nominal alpha for the second interim analysis at 100% to 0.02200. • Removed language regarding additional interim analyses requested by the DSMB.
Section 12.6 (Safety Monitoring)	• Clarified the composition of the PSRT.
Section 14.2 (Site Monitoring)	• Removed text pertaining to local studies conducted in Japan.
Section 20 (Reference List)	• Updated reference list based on changes made to the protocol.
Appendix 2	• Added table numbers to the AESIs of PIMMC and of complications of COVID-19 for cross-reference purposes. • Added reference for Coalition for Epidemic Preparedness Innovations/Brighton Collaboration Consensus Meeting.
General Changes	• Revised text for consistency across the protocol.

Abbreviations: AE = adverse event; AESI = adverse event of special interest; BMI = body mass index; COVID-19 = coronavirus disease 2019; DSMB = Data and Safety Monitoring Board; eDiary = electronic patient-reported outcome diary application; EoS = end of study; HIV = human immunodeficiency virus; IWRS = Interactive web response system; PCR = polymerase chain reaction; PSRT = Protocol Safety Review Team; RNA = ribonucleic acid; SAE = serious adverse event; SARS-CoV-2 rS = severe acute respiratory syndrome coronavirus 2 recombinant spike protein vaccine.

Protocol Version 2.0, 02 October 2020 (revised from Version 1.0, 21 August 2020)

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

Location of Change	Change/Modification in Version 2.0
Title Page	• Matrix-M1™ adjuvant was added to test product because SARS-CoV-2 rS is an adjuvanted vaccine and the 2 products are co-formulated together.
Section 2 (Synopsis - Principal Investigator)	• The Principal Investigator was revised from "To Be Changed" to "This is a multicenter study."
Section 2 (Synopsis - Study Centers)	• The number of study sites was decreased from 300 to approximately 125, and the location of sites outside of North America were condensed to globally (if needed).
Section 2 (Synopsis - Planned Study Period)	• The start of the planned study period was changed from September to October 2020.
Section 2 (Synopsis - Primary Objective); Section 7.1	• Text was added to the primary objective for clarity.
Section 2 (Synopsis - Key Secondary Objective); Section 7.2.1	• Text was added to the key secondary objective for consistency with the text in the primary objective.
Section 2 (Synopsis – Other Secondary Objectives); Section 7.2.2	• Revised name of section to delineate from key secondary objective section. • Added new secondary objective assessing VE against any symptomatic SARS-CoV-2 infection. • Deleted secondary objective on VE of high-risk participants because it was redundant to a subsequent secondary objective. • Added definition of high-risk participants to secondary objective for clarity. • Clarified wording on secondary objectives of efficacy, immunogenicity, safety, mortality, and anti-SARS-CoV-2 NP antibodies. • Clarified that all unsolicited AEs and MAAEs would be assessed from Day 0 through Day 49 and MAAEs attributed to vaccine would be assessed through the EoS. • Added specificity to the secondary objective assessing medical resource utilization. • Added new secondary objective assessing VE against SARS-CoV-2 infection determined by anti-SARS-CoV NP antibodies.
Section 2 (Synopsis - Exploratory Objectives); Section 7.3	• Revised wording of NIH objective for clarity. • Added 2 exploratory objectives pertaining to nasal virus load and sequencing genetic material from SARS-CoV-2 viruses.
Section 2 (Synopsis - Primary Endpoint); Section 7.4	• Text was added to clarify that the primary endpoint would be assessed at the first episode of mild, moderate, or severe COVID-19 with each symptom reported for at least 2 consecutive days. • Removed 48-hour durations for headache and nausea, vomiting or diarrhea based on the change in the endpoint text requiring each symptom to be reported for at least 2 consecutive days.

Location of Change	Change/Modification in Version 2.0
Section 2 (Synopsis - Key Secondary Endpoint); Section 7.5.1	• Text was added to clarify the key secondary endpoint for consistency with the primary endpoint and to cross-reference the same information that is included in the primary endpoint for moderate and severe COVID-19.
Section 2 (Synopsis - Other Secondary Endpoints); Section 7.5.2	• Added new secondary endpoint corresponding to the new secondary objective assessing VE against any symptomatic SARS-CoV-2 infection. • Revised secondary endpoints based on changes made to secondary objectives. • Added secondary endpoint corresponding to the description of the course, treatment, and severity of COVID-19. • Clarified that the injection site reactions of swelling and induration are synonymous, separated arthralgia and myalgia and added systemic reactogenicity reactions of headache and nausea/vomiting. • Added secondary endpoints of unsolicited AEs, MAAEs, SAEs, and AESIs to correspond with the associated secondary objective. • Removed secondary endpoint pertaining to severity of reactogenicity as this endpoint is covered under the other reactogenicity endpoint. • Added secondary endpoint on death due to any cause to correspond with mortality objective. • Added secondary endpoint on antibodies to SARS-CoV-2 NP to correspond with new secondary objective.
Section 2 (Synopsis - Exploratory Endpoints); Section 7.6	• The designated subset of 1,600 Immunogenicity Population participants for NIAID testing was increased to approximately 4,500 participants based on feedback from the CoVPN and OWS external statistics groups. • Added clarifying text to the NIAID endpoint. • Added 2 exploratory endpoints corresponding to the added secondary objectives pertaining to nasal virus load and sequencing genetic material from SARS-CoV-2 viruses.
Section 2 (Synopsis - Study Design)	• Clarified the age strata as 18 to 64 years and ≥ 65 years. • Removed text implying that the Phase 3 study could commence with the younger age cohort (18 to 64 years) based on feedback from OWS. OWS requires that both age strata be initiated concurrently. • Added that 25% of the study population will be ≥ 65 years. • Further defined the high-risk participant population and added the targeted percentage of older participants based on OWS feedback. • Clarified that the selected dose level of SARS-CoV-2 rS with Matrix-M1 adjuvant was based on optimal safety and immunogenicity data from nonclinical and early clinical data. • Clarified that the eDiary would collect solicited AEs of reactogenicity, AEs, and COVID-19 symptomatology, participants will be trained on the eDiary at the initiation of the study, and a Help Desk will be available for eDiary technical issue and the study site for data entry issues. • Clarified the timing of safety assessments during the first 12 months of follow-up post final vaccination and during the second 12 months of follow-up post final vaccination. • Defined the serologic assessments in the study. • The number of participants in the Immunogenicity Population was corrected to 1,600 and text was added to clarify the representative study population. • Added that participants who have a PCR-positive nasal swab indicating SARS-CoV-2 infection at baseline will have SARS-CoV-2 S protein immune responses analyzed, but that these data will not contribute to the primary immunogenicity or

Location of Change	Change/Modification in Version 2.0
	efficacy analyses. • Clarified the recording of other relevant symptoms in the eDiary and noted that participants will be contacted by phone if they are not compliant with it. • Added instructions on nasal swab maintenance and shipping. • Removed text regarding providing all participants with pulse oximeters at enrollment. • Added Unscheduled Illness and Unscheduled Convalescent Visits to monitor participants with PCR-confirmed COVID-19 and added Unscheduled General Visit for all other medical issues. • Clarified the EoS visit. • Added text encouraging participants to continue in the study to follow safety and reported COVID-19 cases. • Added text summarizing the safety monitoring in the study. • Clarified the requirements for vaccination of placebo participants in case the Novavax vaccine or another product are approved by regulatory authorities.
Section 2 (Synopsis - Inclusion Criteria); Section 8.3.1	• Removed males or females from Inclusion Criterion 1 as the text is not needed. • Added text to Inclusion Criterion 1 to specify enrollment of participants who are at substantial risk of exposure or infection with SARS-CoV-2 to ensure enough endpoint events are captured for the primary analysis. • Clarified the definition of female participants of childbearing potential in Inclusion Criterion 3.
Section 2 (Synopsis - Exclusion Criteria); Section 8.3.2	• Clarified Exclusion Criteria 1, 3, 5, and 7. • Revised Exclusion Criterion 4 to exclude participants who received influenza vaccine or any other adult vaccine within 4 days prior to or within 7 days after each study vaccination to avoid confounding reactogenicity observations. • Revised Exclusion Criterion 5 to specify conditions requiring ongoing immunomodulatory therapy and revised the definition of diabetes mellitus. • Removed prior Exclusion Criterion 8 as it is captured under other conditions posing a health risk to participants. • Revised new Exclusion Criterion 8 to broaden the study population by allowing participants with a history of active cancer beyond 1 year instead of 5 years. • Revised Exclusion Criterion 9 to removed latex allergy as a contraindication because there is no latex in contact with the product/injection. • Revised Exclusion Criterion 10 to broaden the study population by allowing participants who plan to become pregnant 3 months after the second vaccination consistent with the respective Inclusion Criterion 3.
Section 2 (Synopsis - Test Product, Dose and Mode of Administration)	• Changed "up to" 2 IM injections to 2 IM injections to clarify that planned vaccination consists of 2 doses. • Added "+ 7 days" to the Day 21 vaccination day.
Section 2 (Synopsis - Reference Therapy, Dose and Duration of Administration)	• Added "normal saline" as the definition of placebo for clarity.
Section 2 (Synopsis - Statistical Methods and Sample Size Calculations)	• The addition of the second interim analysis increased the target number of PCR-confirmed SARS-CoV-2 infections from 141 to 144. • Briefly summarized the 2 formal interim analyses of efficacy and futility that will be conducted based on the accumulation of approximately 50% and 75% of the total anticipated primary endpoints.

Location of Change	Change/Modification in Version 2.0
Section 2 (Synopsis [Intent-to-Treat Efficacy (ITT-EFF) and Immunogenicity (ITT-IMM) Analysis Sets]); Section 12.2.1	• Revised the Analysis Sets for ITT-EFF and ITT-IMM due to changes made in the PP-EFF and PP-IMM Analysis Sets.
Section 2 (Synopsis [Full Analysis Efficacy (FAS-EFF) and Immunogenicity (FAS-IMM) Analysis Sets]); New Section 12.2.2	• Added FAS-EFF and FAS-IMM Analysis Sets for supportive analyses.
Section 2 (Synopsis [Per-Protocol Efficacy (PP-EFF) and Immunogenicity (PP-IMM) Analysis Sets]); Section 12.2.4	• Revised PP-EFF and PP-IMM Analysis Sets to clarify that no major protocol deviations were to occur prior to the first COVID-19 positive episode and to exclude participants with confirmed infection or prior infection due to SARS-CoV-2 at baseline from the PP populations.
Section 2 (Synopsis - Primary Endpoint); Section 12.3.1	• Added country and age strata in the primary endpoint analysis. • Added that cases are to be counted starting 7 days after the second vaccination (Day 28). • Clarified hypothesis testing for VE including revision of statistical methodology.
Section 2 (Synopsis - Secondary Endpoints); Section 12.3.2	• Updated the key secondary and other efficacy endpoint analyses. • Clarified the immunogenicity assessments to be analyzed. • Removed the analysis of SCR. • Added country and vaccine lot to the secondary endpoint analyses.
Section 2 (Synopsis - Safety Analyses); Section 12.3.5	• Added that safety data will be reviewed weekly by the 2019nCoV-301 PSRT to detect possible signals of solicited and unsolicited AEs.
Section 2 (Synopsis - Interim Analyses); Section 12.4	• Added second planned interim analysis and revised timing of both planned interim analyses from 66.7% (original planned analysis) to 50% and 75%, respectively of the targeted total number of cases. • Updated the statistical methods around this analysis based on feedback from the DSMB. • Added text regarding the DSMB's ability to request additional safety and efficacy analyses during the study based on feedback received from the DSMB and OWS.
Section 2 (Synopsis - Monitoring Potential Vaccine Harm); Section 12.5	• Added new section to monitor the study for potential vaccine harm on imbalance in the primary efficacy endpoint.
Section 2 (Synopsis - Data and Safety and Monitoring Board); Section 12.7	• Changed section title from Data Monitoring Committee to Data and Safety Monitoring Board. • Removed duplicate text regarding the treatment of placebo participants with an approved vaccine. • Added text regarding additional functions of the DSMB.

Location of Change	Change/Modification in Version 2.0
Section 3 (Schedule of Assessments)	• Added Unscheduled Illness and Unscheduled Convalescent Visits to monitor participants with PCR-confirmed COVID-19 and changed Unscheduled visit to Unscheduled General Visit for all other medical issues. • Added minimum days following most recent vaccination to Months 6, 12, 18, and 24 visits. • Clarified medical history to medical and social history. • Removed prior/concomitant medications, vital sign measurements, blood sampling for SARS-CoV-2 anti-NP antibodies, and any MAAE attributed to vaccine assessments from the screening visit. • Added blood sampling for SARS-CoV-2 anti-NP antibodies to the Day 0 visit • Added prior/concomitant medications; targeted physical examination; blood sampling for SARS-CoV-2 anti-NP antibodies and immunogenicity; and unsolicited AEs, MAAEs, MAAEs since last visit, MAAEs attributed to vaccine, SAEs, and AESIs to the Unscheduled Acute Illness and Unscheduled Convalescent Visits. • Added footnote at Month 3 visit limiting assessment of unsolicited AEs and MAAEs to Day 49 for clarity. • Added nasal swab at clinic to the Unscheduled Acute Illness Visit. • Added Endpoint Review assessments to the Unscheduled Convalescent Visit. • Added prior/concomitant medications and MAAEs attributed to vaccine to the 18- and 24-Month visits for clarity. • Added text describing when the participant should nasal self-swab and assess oxygen saturation during the study. • Updated nasal swab collection area to anterior nares only. • Updated SoA list of abbreviations. • Updated SoA footnotes based on changes made to the synopsis/body of the protocol.
Section 5 (List of Abbreviations)	• The list of abbreviations was updated based on changes made to the synopsis/body of the protocol.
Section 6.1 (Background)	• Removed "NVXCoV2373" terminology since NVX-CoV2373 represents both the antigen (SARS-CoV-2 rS) and adjuvant (Matrix-M1) and is not used elsewhere in this document for clarity. • Changed "up to" 2 IM injections to 2 IM injections to clarify that planned vaccination consists of 2 doses. • Added "+ 7 days" to the Day 21 vaccination day. • Removed repetitive text regarding the treatment of placebo participants with an approved vaccine.
Section 6.2 (Nonclinical Summary)	• Updated dose-titration studies in various animal models. • Added journal reference to Phase 1 clinical trial.
Section 6.3 (Clinical Summary)	• Clarified Phase 1 (Part 1) text and added information on the Phase 2 (Part 2) study.

Location of Change	Change/Modification in Version 2.0
Section 6.4 (Study Rationale)	• Clarified Phase 1 (Part 1) text and added journal reference for Phase 1 study. • Added summary of Phase 2 (Part 2) reactogenicity data. • Removed text implying that the Phase 3 study could commence with the younger age cohort (18 to 64 years) based on feedback from OWS. OWS requires that both age strata be initiated concurrently. • Changed "up to" 2 IM injections to 2 IM injections to clarify that planned vaccination consists of 2 doses. • Added "+ 7 days" to the Day 21 vaccination day. • Added text regarding the treatment of placebo participants with an approved vaccine.
Section 6.5 (Rationale for Dose Selection)	• Added journal reference for Phase 1 study.
Section 6.6 (Benefit – Risk Assessment)	• Updated Benefit-Risk section to add that antigen is not produced using infectious SARS-CoV-2. • Added mitigation approach to AEs related to hypersensitivity with text from the IB.
Section 6.6.2 (Overall Benefit – Risk Conclusion)	• Added Phase 2 (Part 2) safety data that showed a similar reactogenicity profile between younger and older participants, with both local and systemic reactogenicity events generally occurring less frequently in older adults.
Section 8.1 (Study Design Description)	• Clarified the age strata as 18 to 64 years and ≥ 65 years. • Removed text implying that the Phase 3 study could commence with the younger age cohort (18 to 64 years) based on feedback from OWS. OWS requires that both age strata be initiated concurrently. • Clarified that the majority of participants will be consented, enrolled and vaccinated on Day 0. • Further defined the high-risk participant population and added the targeted percentage of older participants based on OWS feedback. • Specified race and ethnicity to ensure a diverse study population. • Clarified that the selected dose level of SARS-CoV-2 rS with Matrix-M1 adjuvant was based on optimal safety and immunogenicity data from nonclinical and early clinical data. • Clarified that the eDiary would collect solicited AEs of reactogenicity, AEs, and COVID-19 symptomatology, participants will be trained on the eDiary at the initiation of the study, and a Help Desk will be available for eDiary technical issue and the study site for data entry issues. • Clarified the timing of safety assessments during the first 12 months of follow-up post final vaccination and during the second 12 months of follow-up post final vaccination. • Defined the serologic assessments in the study. • The number of participants in the Immunogenicity Population was corrected to 1,600 and text was added to clarify the representative study population. • Added that participants who have a PCR-positive nasal swab indicating SARS-CoV-2 infection at baseline will have SARS-CoV-2 S protein immune responses analyzed, but that these data will not contribute to the primary immunogenicity or efficacy analyses. • Clarified the recording of other relevant symptoms in the eDiary and noted that participants will be contacted by phone if they are not compliant with it. • Added instructions on nasal swab maintenance and shipping. • Removed text regarding providing all participants with pulse oximeters at

Location of Change	Change/Modification in Version 2.0
	enrollment. • Added Unscheduled Illness and Unscheduled Convalescent Visits to monitor participants with PCR-confirmed COVID-19 and added Unscheduled General Visit for all other medical issues. • Clarified the EoS visit. • Added text encouraging participants to continue in the study to follow safety and reported COVID-19 cases. • Added text summarizing the safety monitoring in the study. • Clarified the requirements for vaccination of placebo participants in case the Novavax vaccine or another product are approved by regulatory authorities. • Removed duplicate text regarding the treatment of placebo participants with an approved vaccine. • Added text regarding additional functions of the DSMB.
Section 8.2 (Discussion of Study Design)	• Revised text for consistency with the changes made to the Study Design section for clarity.
Section 8.2.2 (Trial Vaccine After the End of Study)	• Revised text regarding the treatment of placebo participants with an approved vaccine for consistency with similar text in the Study Design section.
Section 8.4 (Prohibited Medications)	• Added criteria for prohibiting administration of seasonal influenza vaccine during the study.
Section 8.6 (Strategies for Recruitment and Retention)	• Updated section for consistency with the Study Design section and added specifics regarding the percentage of high-risk participants that should be targeted for enrollment into the study.
Old Section 8.8 (Unscheduled Visits)	• Moved section to Efficacy Assessments (Section 10.1.2).
New Section 8.8 (Trial Vaccine Discontinuation and Participant Discontinuation/ Withdrawal)	• Section title was revised to include participant discontinuation and withdrawal. • Subsections were added to clarify reasons for trial vaccine discontinuation, temporary discontinuation/vaccine pause, and withdrawal of participants by participants, investigator, and Sponsor.
Section 9 (Study Treatment)	• Revised text for clarity. • Moved Study Treatment Accountability section to end of section.
Section 10.1 (Efficacy Assessments)	• Revised text for consistency with Study Design section and added descriptions of the Unscheduled Acute Illness and Unscheduled Convalescent Visits for assessment and monitoring of confirmed cases of symptomatic COVID-19. • Added description of nasal swabs for virus detection, • Added text on when participants will be instructed on the FLU-PRO questionnaire. • Added text on the number of participants who completed the FLU-PRO for historical reference.
Section 10.2 (Immunogenicity Assessments)	• Defined the serologic assessments in the study. • The number of participants in the Immunogenicity Population was corrected to 1,600 and text was added to clarify the representative study population.
Section 10.3.1.2 (Events Meeting the AE Definition)	• Signs, symptoms, or clinical sequelae of a suspected overdose were removed from this section because overdose was already described in Section 10.3.10 of the protocol.

Location of Change	Change/Modification in Version 2.0
Section 10.3.1.7 (Reactogenicity Symptoms)	• Added cross-reference to FDA toxicity criteria for assessment of severity, which can be found in Appendix 4.
Section 10.3.2 (Time Period and Frequency for Collecting AE and SAE Information)	• Clarified that all AEs reported or observed during the study will be recorded on the AE page of the eCRF. • Clarified that MAAEs attributed to vaccine (not MAAEs) would be assessed through the EoS.
Section 10.3.4.1 [Assessment of Intensity (Severity)]	• Replaced severity criteria used to assess reactogenicity with standard severity criteria for unsolicited AEs.
Section 10.3.6.2 (Safety Reporting to Health Authorities, Independent Ethics Committees/ Institutional Review Boards and Investigators)	• Text revised to state that Novavax will have responsibility for safety reporting to the US FDA and ICON for all other reporting.
Section 10.3.8 (Physical Examination)	• Added text that weight and BMI would be re-assessed if clinically indicated.
Section 10.3.9 (Vital Signs)	• Corrected body temperature that should not be exceeded from 30°C to 38°C.
Old Section 10.4 (Study Halting Rules)	• The contents of this section were moved to revised Trial Vaccine Discontinuation and Participant Discontinuation/Withdrawal.
Section 10.3.10 (Overdose)	• Clarified the reporting of overdose as either an AE or SAE.
New Section 10.4 (Other Assessments)	• New section added to describe assessments not related to efficacy and safety, including description of the eDiary.
Section 11 (Medical Resource Utilization)	• Title and content of section was revised to focus on medical resource allocation for consistency with the efficacy endpoints of the study.
Section 12.1 (Sample Size and Power)	• The addition of the second interim analysis increased the target number of PCR-confirmed SARS-CoV-2 infections from 141 to 144. • Added second planned interim analysis and revised timing of both planned interim analyses from 66.7% (original planned analysis) to 50% and 75%, respectively of the targeted total number of cases. • Updated the estimated power calculations based on the changes made to the planned interim analyses. • Described the rationale for the sample size of the Immunogenicity Population. • Added description of two-stage random samplings to facilitate the case-cohort sampling design.
Section 12.3.3 (Statistical Models)	• Added country and age strata as covariates. • Revised that cases were to be counted starting 7 days (not 14 days) after the second vaccination. • Added Cox proportional hazards model description.
Section 12.3.4 (Handling of Missing Data)	• Section was revised for clarity.

Location of Change	Change/Modification in Version 2.0
Section 12.6 (Safety Monitoring)	• Added new section describing the safety monitoring in the study.
Section 14.2 (Site Monitoring)	• Removed text pertaining to local studies conducted in Japan.
Section 15.1 (Case Report Forms/Source Data Handling)	• Revised text for clarity. • Removed laboratory test text since no clinical laboratory tests will be performed in the study.
Section 17 (Publication Policy)	• Added text providing authors reasonable access to all study data, statistical tables, figures and relevant reports to review complete study results.
Section 19 (Signature of Investigator)	• Section was updated for clarity.
Section 20 (Reference List)	• Updated reference list based on changes made to the protocol.
Section 21 (Appendices)	• Added an appendix (Appendix 1) to list the changes to the protocol. • Added an appendix (Appendix 3) providing example stopping bounds for vaccine harm monitoring. • Added an appendix (Appendix 4) providing the FDA grading scale for local and general reactogenicity.
General Changes	• Matrix-M adjuvant changed to Matrix-M1 adjuvant, where applicable because that is the specific adjuvant used in the trial. • Corrected use of abbreviations in text by defining abbreviations at first use and applying abbreviations they have been defined. • Revised text for consistency across the protocol.

Abbreviations: AE = adverse event; AESI = adverse event of special interest; BMI = body mass index; COVID-19 = coronavirus disease 2019; CoVPN = COVID-19 Prevention Network; DSMB = Data and Safety Monitoring Board; eDiary = electronic patient-reported outcome diary application; EoS = end of study; FAS-EFF = Full Analysis Set – Efficacy; FAS-IMM = Full Analysis Set – Immunogenicity; FDA = United States Food and Drug Administration; FLU-PRO = InFLUenza Patient-Reported Outcome (questionnaire); IB = Investigator's Brochure; IM = intramuscular; ITT-EFF = Intent-to-Treat – Efficacy; ITT-IMM = Intent-to-Treat – Immunogenicity; MAAE = medically attended adverse event; NP = nucleocapsid; OWS = Operation Warp Speed; PP-EFF = Per Protocol – Efficacy; PP-IMM = Per Protocol – Immunogenicity; PCR = polymerase chain reaction; PSRT = Protocol Safety Review Team; 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 vaccine; SCR = seroconversion response; SoA = Schedule of Assessments; VE = vaccine efficacy.

Appendix 2: Listings of Adverse Events of Special Interest

Because it has been hypothesized that immunizations with or without adjuvant may be associated with autoimmunity, regulatory authorities have requested that Novavax instruct investigators to be especially vigilant regarding the PIMMC listed below (Table 7). Note that this regulatory request is not specific to Novavax's SARS-CoV-2 rS or Matrix-M1 adjuvant; and there is no current evidence to suggest that the trial vaccines in this protocol are, or are not, associated with these illnesses. The list is not intended to be exhaustive, nor does it exclude the possibility that other diagnoses may be AESI.

Table 7 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.

Table 7 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 (Table 8). The list is not intended to be exhaustive, nor does it exclude the possibility that other diagnoses may be AESI.

Table 8 Adverse Events Representing Complications Specific to of COVID-19[1]	
Categories	**Diagnoses (as MedDRA System Organ Class/Preferred Term)**
Respiratory/Infectious Disorders:	ARDS, pneumonitis, septic shock-like syndrome.
Cardiac Disorders:	Acute cardiac injury, arrhythmia.
Coagulopathy	Deep vein thrombosis, myocardial infarction, stroke.
Renal Disorders:	Acute kidney injury.
Hematologic Disorder	Thrombocytopenia, septic shock-like syndrome.
Inflammatory Disorders:	Cytokine Release Syndrome related to COVID-19 infection[2], multisystem inflammatory syndrome in children (MIS-C).
Neurologic Disorders:	Generalized convulsions.

Abbreviations: ARDS = acute respiratory distress syndrome; COVID-19 = coronavirus disease 2019; DAIDS = Division of AIDS; MedDRA = Medical Dictionary for Regulatory Activities.

1. COVID-19 manifestations associated with more severe presentation and decompensation with consideration of enhanced disease potential. The current listing is based on Coalition for Epidemic Preparedness Innovations /Brighton Collaboration Consensus Meeting (12/13 March 2020) and expected to evolve as evidence accumulates [Lambert 2020].
2. Cytokine release syndrome related to COVID-19 infection is a disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath [DAIDS, 2017].

Appendix 3: Example Stopping Bounds for Vaccine Harm Monitoring

Example stopping bounds for harm monitoring based on the randomization ratio. Each test is based on exact binomial test given the total number of cases at one-sided alpha = 0.05 under H0: p = 0.67 (corresponds to VE = 0).

Placebo Cases	Active Cases	Total Cases	Proportion of Cases in Active Group	One-sided Lower Exact 95% CI
0	8	8	1.000	0.688
1	12	13	0.923	0.684
2	15	17	0.882	0.674
3	18	21	0.857	0.671
4	21	25	0.840	0.670
5	24	29	0.828	0.671
6	27	33	0.818	0.672
7	30	37	0.811	0.674
8	32	40	0.800	0.668
9	35	44	0.795	0.670
10	38	48	0.792	0.672
11	40	51	0.784	0.668
12	43	55	0.782	0.671
13	46	59	0.780	0.673
14	48	62	0.774	0.670
15	51	66	0.773	0.672
16	53	69	0.768	0.669
17	56	73	0.767	0.671
18	58	76	0.763	0.669
19	61	80	0.763	0.671
20	63	83	0.759	0.669
21	65	86	0.756	0.668
22	68	90	0.756	0.670
23	70	93	0.753	0.668
24	73	97	0.753	0.670
25	75	100	0.750	0.669
26	78	104	0.750	0.670
27	80	107	0.748	0.669
28	82	110	0.745	0.668
29	85	114	0.746	0.670
30	87	117	0.744	0.669
31	89	120	0.742	0.668
32	92	124	0.742	0.669
33	94	127	0.740	0.668

Placebo Cases	Active Cases	Total Cases	Proportion of Cases in Active Group	One-sided Lower Exact 95% CI
34	97	131	0.740	0.670
35	99	134	0.739	0.669
36	101	137	0.737	0.668
37	104	141	0.738	0.670

Appendix 4: FDA Toxicity Grading Scale for Local and General Systemic Reactogenicity

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

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

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

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

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

Source: [DHHS 2007].