

CLINICAL STUDY PROTOCOL

A PHASE 2A/B, RANDOMIZED, OBSERVER-BLINDED, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY, IMMUNOGENICITY, AND SAFETY OF A SARS-CoV-2 RECOMBINANT SPIKE PROTEIN NANOPARTICLE VACCINE (SARS-CoV-2 rS) WITH MATRIX-M1™ ADJUVANT IN SOUTH AFRICAN ADULT SUBJECTS LIVING WITHOUT HIV; AND SAFETY AND IMMUNOGENICITY IN ADULTS LIVING WITH HIV

PROTOCOL NO. 2019nCoV-501

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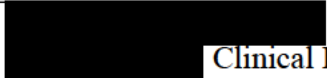
The concepts and information contained in this document or generated during the study are considered proprietary and may not be disclosed in whole or in part without the expressed, written consent of Novavax, Inc.

The study will be conducted according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guideline E6(R2): Good Clinical Practice.

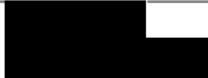
SIGNATURE PAGE

PROTOCOL TITLE: A Phase 2a/b, Randomized, Observer-Blinded, Placebo-Controlled Study to Evaluate the Efficacy, Immunogenicity, and Safety of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine (SARS-CoV-2 rS) With Matrix-M1™ Adjuvant in South African Adults Living Without HIV; and Safety and Immunogenicity in Adults Living With HIV

PROTOCOL NUMBER: 2019-nCoV-501


Clinical Development
Novavax, Inc.

Date


Clinical Operations
Novavax, Inc.

Date

INVESTIGATOR PROTOCOL AGREEMENT PAGE

I agree to conduct the study as outlined in the protocol titled “A Phase 2a/b, Randomized, Observer-Blinded, Placebo-Controlled Study to Evaluate the Efficacy, Immunogenicity, and Safety of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine (SARS-CoV-2 rS) With Matrix-M1™ Adjuvant in South African Adult Subjects Living Without HIV; and Safety and Immunogenicity in Adults Living With HIV” in accordance with all guidelines, including International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines, and all applicable government regulations. I have read and understand all sections of the protocol.

Signature of Investigator

Date

Printed Name of Investigator

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PROTOCOL SYNOPSIS

PROTOCOL NO.: 2019nCoV-501

TITLE: A Phase 2a/b, Randomized, Observer-Blinded, Placebo-Controlled Study to Evaluate the Efficacy, Immunogenicity, and Safety of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine (SARS-CoV-2 rS) With Matrix-M1™ Adjuvant in South African Adults Living Without HIV; and Safety and Immunogenicity in Adults Living With HIV

STUDY PHASE: Phase 2a/b

STUDY SITES: Up to 15 clinical sites across South Africa.

OBJECTIVES:

Cohort 1: HIV-Negative Subjects

- **The primary objectives are:**
 - To evaluate the efficacy of SARS-CoV-2 rS with Matrix-M1 adjuvant compared to placebo on the occurrence of symptomatic mild, moderate, or severe confirmed coronavirus disease 2019 (COVID-19) as demonstrated by qualitative polymerase chain reaction (PCR) in serologically naïve (to severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) healthy human immunodeficiency virus (HIV)-negative adult subjects.
 - To evaluate the efficacy of SARS-CoV-2 rS with Matrix-M1 adjuvant compared to placebo on the occurrence of symptomatic moderate or severe confirmed COVID-19 as demonstrated by qualitative PCR in serologically naïve (to SARS-CoV-2) healthy HIV-negative adult subjects.
 - To accumulate and describe the safety experience for SARS-CoV-2 rS with Matrix-M1 adjuvant based on solicited short-term reactogenicity across a broad age spectrum (by toxicity grade) and by adverse event (AE) profile for vaccination through Day 35 in healthy HIV-negative adult subjects regardless of baseline serostatus and stratified by baseline serostatus.
- **The secondary objectives are:**
 - To evaluate the efficacy of SARS-CoV-2 rS with Matrix-M1 adjuvant compared to placebo on the occurrence of individual strata of symptomatic virologically confirmed, mild, moderate, or severe categories of confirmed COVID-19 as demonstrated by qualitative PCR in serologically naïve (to SARS-CoV-2) healthy HIV-negative adult subjects.
 - To evaluate the efficacy of SARS-CoV-2 rS with Matrix-M1 adjuvant compared to placebo on the occurrence of hospitalization (regardless of severity) with confirmed COVID-19 as demonstrated by qualitative PCR in serologically naïve (to SARS-CoV-2) healthy HIV-negative adult subjects.

- To assess incidence, severity, and symptom duration of SARS-CoV-2 infection and to describe the characteristics of subjects with symptomatic virologically confirmed, mild, moderate, and/or severe COVID-19 in serologically naïve (to SARS-CoV-2) healthy HIV-negative adult subjects, overall and by age strata.
- To assess the immune response (immunoglobulin G [IgG] antibody to SARS-CoV-2 rS protein and angiotensin-converting enzyme 2 (ACE2) receptor binding inhibition) for SARS-CoV-2 rS with Matrix-M1 adjuvant at Day 21 (post first dose), Day 35 (post second dose), and across later study time points in serologically naïve (to SARS-CoV-2) healthy HIV-negative adult subjects, regardless of baseline serostatus and stratified by baseline serostatus (to SARS-CoV-2).
- To describe the amplitude, kinetics, and durability of immune response in terms of enzyme-linked immunosorbent assay (ELISA) units of serum IgG antibodies and titers of ACE2 receptor binding inhibition to SARS-CoV-2 rS protein(s) at selected time points and relative to whether subjects had pre-existing antibodies to SARS-CoV-2, regardless of baseline serostatus and stratified by baseline serostatus (to SARS-CoV-2). To include reverse cumulative distribution curves.
- To describe the immune response to the primary 2-dose regimen of SARS-CoV-2 rS with Matrix-M1 adjuvant in terms of titers of neutralizing antibody at selected study time points in a subset of healthy HIV-negative adult subjects, regardless of baseline serostatus and stratified by baseline serostatus (to SARS-CoV-2).
- To assess overall safety through Day 35 for all AEs and through the end of study (EOS) for any medically attended adverse event (MAAE) attributed to vaccine, adverse event(s) of special interest (AESI), or serious adverse event (SAE) in healthy HIV-negative adult subjects regardless of baseline serostatus and stratified by baseline serostatus.
- **The exploratory objectives are:**
 - To evaluate the efficacy of SARS-CoV-2 rS with Matrix-M1 adjuvant compared to placebo on the occurrence of symptomatic virologically confirmed; symptomatic mild, moderate, or severe; OR symptomatic moderate or severe confirmed COVID-19 as demonstrated by qualitative PCR in healthy HIV-negative adult subjects, serologically naïve (to SARS-CoV-2) at **baseline and regardless of baseline** serological status to SARS-CoV-2, and following the **first or second dose** of study vaccine, overall and by age strata.
 - To evaluate the efficacy of SARS-CoV-2 rS with Matrix-M1 adjuvant compared to placebo on the occurrence of serological evidence of SARS-CoV-2 infection as measured by a multiplex serological assay that measures the immune response to one or more non-vaccine SARS-CoV-2 viral antigens (eg, anti-nucleocapsid [anti-N] antibodies) at baseline and at selected time points (in order to distinguish between serological responses to vaccine versus natural infection). Responses to non-vaccine SARS-CoV-2 viral antigens will be described at selected time points. Note, responses to vaccine-related SARS-CoV-2 viral antigens (eg, spike protein and related epitopes) reported on this multiplex serological assay may be

described for qualitative purposes but will not be used to describe the primary or secondary immunogenicity endpoints.

Cohort 2: HIV-Positive Subjects

- **The primary objectives are:**
 - To accumulate and describe the safety experience for SARS-CoV-2 rS with Matrix-M1 adjuvant based on solicited short-term reactogenicity across a broad age spectrum (by toxicity grade) and by AE profile for vaccination through Day 35 in medically stable HIV-positive adult subjects regardless of baseline serostatus and stratified by baseline serostatus.
 - To assess the immune response (IgG antibody to SARS-CoV-2 rS protein) for SARS-CoV-2 rS with Matrix-M1 adjuvant at Day 35 and whether baseline immune status (to SARS-CoV-2) has an impact in medically stable HIV-positive adult subjects (ie, regardless of baseline serostatus and stratified by baseline serostatus).
- **The secondary objectives are:**
 - To assess overall safety through Day 35 for all AEs and through the EOS for any MAAE attributed to vaccine, AESI, or SAE in medically stable HIV-positive adult subjects regardless of baseline serostatus and stratified by baseline serostatus.
 - To assess the immune response (IgG antibody to SARS-CoV-2 rS protein and ACE2 receptor binding inhibition) for SARS-CoV-2 rS with Matrix-M1 adjuvant at Day 21 (post first dose), Day 35 (post second dose), and across later study time points in medically stable HIV-positive adult subjects, regardless of baseline serostatus and stratified by baseline serostatus (to SARS-CoV-2).
 - To describe the amplitude, kinetics, and durability of immune response in terms of ELISA units of serum IgG antibodies and titers of ACE2 receptor binding inhibition to SARS-CoV-2 rS protein(s) at selected time points and relative to whether subjects had pre-existing antibodies to SARS-CoV-2 (ie, regardless of baseline serostatus and stratified by baseline serostatus). To include reverse cumulative distribution curves.
 - To describe the immune response to the primary 2-dose regimen of SARS-CoV-2 rS with Matrix-M1 adjuvant in terms of titers of neutralizing antibody at selected study time points in a subset of medically stable HIV-positive adult subjects, regardless of baseline serostatus and stratified by baseline serostatus (to SARS-CoV-2).
 - To describe the incidence of symptomatic virologically confirmed, mild, moderate, or severe confirmed COVID-19 as demonstrated by qualitative PCR in serologically naïve (to SARS-CoV-2) medically stable HIV-positive adult subjects.

- To describe the incidence of symptomatic moderate or severe confirmed COVID-19 as demonstrated by qualitative PCR in serologically naïve (to SARS-CoV-2) medically stable HIV-positive adult subjects.
- To assess severity and symptom duration of SARS-CoV-2 infection and to describe the characteristics of subjects with symptomatic virologically confirmed, mild, moderate, and/or severe COVID-19 in serologically naïve (to SARS-CoV-2) medically stable HIV-positive adult subjects.
- **The exploratory objectives are:**
 - To evaluate the efficacy of SARS-CoV-2 rS with Matrix-M1 adjuvant compared to placebo on the occurrence of symptomatic virologically confirmed; symptomatic mild, moderate, or severe; OR symptomatic moderate or severe confirmed COVID-19 as demonstrated by qualitative PCR in medically stable HIV-positive adult subjects, serologically naïve (to SARS-CoV-2) at baseline and regardless of baseline serological status to SARS-CoV-2, and following the first or second dose of study vaccine.
 - To describe the immune responses (IgG antibody, ACE2 receptor binding inhibition, and neutralizing antibody) to SARS-CoV-2 rS with Matrix-M1 adjuvant in HIV-positive subjects according to baseline levels of CD4+ counts and/or HIV viral load, at Day 35 and at selected study time points.
 - To describe the immune responses (IgG antibody, ACE2 receptor binding inhibition, and neutralizing antibody) to SARS-CoV-2 rS with Matrix-M1 adjuvant in HIV-positive subjects relative to HIV-negative subjects at Day 35 and at selected study time points, regardless of baseline serostatus and stratified by baseline serostatus (to SARS-CoV-2).
 - To evaluate the efficacy of SARS-CoV-2 rS with Matrix-M1 adjuvant compared to placebo on the occurrence of serological evidence of SARS-CoV-2 infection as measured by a multiplex serological assay that measures the immune response to one or more non-vaccine SARS-CoV-2 viral antigens (eg, anti-N antibodies) at baseline and at selected time points (in order to distinguish between serological responses to vaccine versus natural infection). Responses to non-vaccine SARS-CoV-2 viral antigens will be described at selected time points. Note, responses to vaccine-related SARS-CoV-2 viral antigens (eg, spike protein and related epitopes) reported on this multiplex serological assay may be described for qualitative purposes but will not be used to describe the primary or secondary immunogenicity endpoints.

ENDPOINTS

Cohort 1: HIV-Negative Subjects

- **The primary endpoints are:**

Primary endpoints include 2 independent efficacy endpoints and a safety endpoint.

- **FIRST PRIMARY EFFICACY ENDPOINT:** Positive (+) PCR-confirmed SARS-CoV-2 illness with **symptomatic mild, moderate, or severe COVID-19** (Table S1-1) in serologically naïve (to SARS-CoV-2) healthy HIV-negative adult subjects, with a lower bound confidence interval (CI) of > 0, from 7 days after the second vaccine dose (eg, Day 28) until the endpoint-driven efficacy analysis is triggered by the occurrence of a prespecified number of blinded endpoints across the 2 study vaccine arms and/or at prespecified time points.

Table S1-1 Primary Efficacy Endpoint Definitions of COVID-19 Severity

COVID-19 Severity	Endpoint Definitions
Virologically Confirmed	≥ 1 COVID-19 disease symptom in Table S1-2 AND Does not meet criteria for mild, moderate, or severe disease
Mild	≥ 1 of: <ul style="list-style-type: none"> • Fever (defined by subjective or objective measure, regardless of use of anti-pyretic medications) • New onset cough • ≥ 2 COVID-19 respiratory/non-respiratory symptoms in Table S1-2 AND <ul style="list-style-type: none"> • Does not meet criteria for moderate or severe
Moderate	≥ 1 of: <ul style="list-style-type: none"> • Fever (defined by subjective or objective measure, regardless of use of anti-pyretic medications) + any 2 COVID-19 symptoms in Table S1-2 for ≥ 3 days (need not be contiguous days) • High fever (≥ 38.4°C) for ≥ 3 days (need not be contiguous days) • Any evidence of significant LRTI: <ul style="list-style-type: none"> – Shortness of breath (or breathlessness or difficulty breathing) with or without exertion (greater than baseline) – Tachypnea: 20 to 29 breaths per minute at rest – SpO₂: 94% to 95% on room air – Abnormal chest x-ray or chest CT consistent with pneumonia or LRTI – Adventitious sounds on lung auscultation (eg, crackles/rales, wheeze, rhonchi, pleural rub, stridor) AND <ul style="list-style-type: none"> • Does not meet criteria for severe disease

Table S1-1 Primary Efficacy Endpoint Definitions of COVID-19 Severity

COVID-19 Severity	Endpoint Definitions
Severe	<p>≥ 1 of:</p> <ul style="list-style-type: none"> • Tachypnea: ≥ 30 breaths per minute at rest • Resting heart rate ≥ 125 beats per minute • SpO₂: ≤ 93% on room air or PAO₂/FiO₂ < 300 • High flow oxygen therapy or NIV/NIPPV (eg, CPAP or BiPAP) • Mechanical ventilation or ECMO • One or more major organ system dysfunction or failure (eg, cardiac/circulatory, pulmonary, renal, hepatic, and/or neurological, to be defined by diagnostic testing/clinical syndrome/interventions), including any of the following: <ul style="list-style-type: none"> – ARDS – Acute renal failure – Acute hepatic failure – Acute right or left heart failure – Septic or cardiogenic shock (with shock defined as SBP < 90 mm Hg OR DBP < 60 mm Hg) – Acute stroke (ischemic or hemorrhagic) – Acute thrombotic event: AMI, DVT, PE – Requirement for: vasopressors, systemic corticosteroids, or hemodialysis. • Admission to an ICU • Death

Abbreviations: AMI = acute myocardial infarction; ARDS = acute respiratory distress syndrome; BiPAP = bi-level positive airway pressure; CPAP = continuous positive air pressure; CT = computed tomography; DBP = diastolic blood pressure; DVT = deep vein thrombosis; ECMO = extracorporeal membrane oxygenation; FiO₂ = fraction of inspired oxygen; ICU = intensive care unit; LRTI = lower respiratory tract infection; NIV = non-invasive ventilation; NIPPA = non-invasive positive pressure ventilation; PAO₂ = partial pressure of oxygen in the alveolus; PE = pulmonary embolism; SBP = systolic blood pressure; SpO₂ = oxygen saturation.

Symptomatic COVID-19 is defined as a self-reported acute respiratory/systemic new onset illness that is clinically consistent with COVID-19 based on the presence of fever (defined by subjective or objective measure, regardless of use of anti-pyretic medications) or ≥ 2 respiratory/non-respiratory tract symptoms (Table S1-2). In the case of rapid decompensation to a severe COVID-19 case, emergency department, hospital, or post-mortem data can be used for ascertainment of both clinical endpoint data, and for virologically confirmed positive cases without the initial presentation for case ascertainment and procuring a swab during a COVID-19 Surveillance Visit (Initial and Follow-Up).

Table S1-2 Symptoms of Suspected COVID-19

Respiratory	Non-Respiratory
New onset cough	Fever or feverishness (defined subjectively, or objective fever $\geq 37.8^{\circ}\text{C}$, regardless of use of anti-pyretic medications)
New onset rapid breathing	Myalgia (or muscle ache)
New onset shortness of breath (or breathlessness or difficulty breathing)	Chills
Sore throat	Loss of taste (or taste disturbance)
Loss of smell (or smell disturbance)	Headache
Nasal congestion	Diarrhea
Runny nose	Tiredness (or fatigue or weakness)
	Nausea or vomiting
	Loss of appetite

Abbreviations: COVID-19 = coronavirus disease 2019.

- **SECOND PRIMARY EFFICACY ENDPOINT:** (+) PCR-confirmed SARS-CoV-2 illness with **symptomatic moderate or severe COVID-19** (Table S1-1) in serologically naïve (to SARS-CoV-2) healthy HIV-negative adult subjects, with a lower bound CI > 0, from 7 days after the second vaccine dose (eg, Day 28) until the endpoint-driven efficacy analysis is triggered by the occurrence of a prespecified number of blinded endpoints across the 2 study vaccine arms and/or at prespecified time points.
- **PRIMARY SAFETY ENDPOINTS:** Numbers and percentages (with 95% CIs) of healthy HIV-negative adult subjects with solicited AEs (local, systemic) for 7 days following each vaccination (Days 0 and 21) by severity score, duration, and peak intensity in healthy HIV-negative adult subjects regardless of baseline serostatus and stratified by baseline serostatus. In the case of no toxicity, a score of zero (0) will be applied.

Numbers and percentages (with 95% CI) of subjects with unsolicited AEs (eg, treatment-emergent, serious, suspected unexpected serious, those of special interest, MAAEs) through Day 35 by Medical Dictionary for Regulatory Activities (MedDRA) classification, severity score, and relatedness in healthy HIV-negative adult subjects regardless of baseline serostatus and stratified by baseline serostatus.

- **The secondary endpoints are:**

- (+) PCR-confirmed SARS-CoV-2 with COVID-19 in serologically naïve (to SARS-CoV-2) healthy HIV-negative adult subjects in terms of individual strata of symptomatic virologically confirmed, mild, moderate, or severe categories of COVID-19 as previously described.
- (+) PCR-confirmed SARS-CoV-2 with COVID-19 in serologically naïve (to SARS-CoV-2) healthy HIV-negative adult subjects requiring hospitalization (regardless of severity).
- Incidence, maximum severity score, and symptom duration of SARS-CoV-2 infection by classification of symptomatic virologically confirmed, mild, moderate, and/or severe COVID-19 in serologically naïve (to SARS-CoV-2) healthy HIV-negative adult subjects, overall and by age strata. Should COVID-19 illness scoring be substantially validated at the time of study start, application of the standard scoring may be applied.
- Serum IgG antibody levels specific for the SARS-CoV-2 rS protein antigen(s) as detected by ELISA using geometric mean titers (GMT) OR seroconversion rate (SCR) at Day 21 (post first dose), Day 35 (post second dose), and across later study time points in healthy HIV-negative adult subjects, regardless of baseline serostatus and stratified by baseline serostatus (to SARS-CoV-2).
Derived/calculated endpoints based on these data will include geometric mean ELISA units (GMEUs), geometric mean fold rise (GMFR), and SCR.

SCR is defined as the percentage of subjects with a post-vaccination titer ≥ 4 -fold over naïve background and ≥ 2 -fold over pre-existing titer.

Positive baseline status (+/-) using GMT and/or (+) PCR at baseline.

- Serum IgG antibody levels specific for the SARS-CoV-2 rS protein antigen as detected by ELISA, described across study time points with derived/calculated endpoints to include GMEUs, GMFR, and SCR in healthy HIV-negative adult subjects, regardless of baseline serostatus and stratified by baseline serostatus (to SARS-CoV-2).
- Epitope-specific immune responses to the SARS-CoV-2 rS protein receptor binding domain measured by serum titers in an ACE2 receptor binding inhibition assay, described across study time points, to include GMT, GMFR, SCR, and seroresponse rate (SRR) in healthy HIV-negative adult subjects, regardless of baseline serostatus and stratified by baseline serostatus (to SARS-CoV-2). SRR is defined as the proportion of subjects with rises in titers exceeding the 95th percentile of placebo subjects at the same time point and based on prior SARS-CoV-2 exposure.
- Neutralizing antibody activity at Day 35 and across later study time points relative to baseline in healthy HIV-negative adult subjects by absolute titers and change from baseline, including SCR (≥ 4 -fold change) and SRR, regardless of baseline serostatus and stratified by baseline serostatus (to SARS-CoV-2) to investigate whether baseline status (+/-) impacts response.

- Numbers and percentages (with 95% CI) of subjects with MAAEs, AESI, or SAE through the EOS by MedDRA classification, severity score, and relatedness in healthy HIV-negative adult subjects regardless of baseline serostatus and stratified by baseline serostatus.
- **Exploratory endpoints are:**
 - As previously described in the first and second primary efficacy endpoints for Cohort 1 (HIV-negative subjects) but applied to baseline seronegative and seropositive (to SARS-CoV-2) subjects, combined and separately, and following the first or second dose, and by age strata.
 - One or more non-vaccine SARS-CoV-2 viral antigen-specific immune responses (eg, anti-N antibodies) measured by serum titers/units in an appropriate assay to indicate an interval seroconversion at a given post-vaccination study time point. Descriptive measures will include GMT, GMFR, SCR, and SRR. SRR is defined as the proportion of subjects with rises in antibody units/titers exceeding the 95th percentile of placebo subjects at the same time point and based on prior baseline exposure.

Cohort 2: HIV-Positive Subjects

- **The primary endpoints are:**
 - Numbers and percentages (with 95% CIs) of subjects with solicited AEs (local, systemic) for 7 days following each vaccination (Days 0 and 21) by severity score, duration, and peak intensity in medically stable HIV-positive adult subjects regardless of baseline serostatus and stratified by baseline serostatus. In the case of no toxicity, a score of zero (0) will be applied.
 - Numbers and percentages (with 95% CI) of subjects with unsolicited AEs (eg, treatment-emergent, serious, suspected unexpected serious, those of special interest, MAAEs) through Day 35 by MedDRA classification, severity score, and relatedness in medically stable HIV-positive adult subjects regardless of baseline serostatus and stratified by baseline serostatus.
 - Serum IgG antibody levels specific for the SARS-CoV-2 rS protein antigen(s) as detected by ELISA using GMT OR SCR at Day 35 in medically stable HIV-positive adult subjects regardless of baseline serostatus and stratified by baseline serostatus. Derived/calculated endpoints based on these data will include GMEUs, GMFR, and SCR.

SCR is defined as the percentage of subjects with a post-vaccination titer \geq 4-fold over naïve background and \geq 2-fold over pre-existing titer.

Positive baseline status (+/-) using GMT and/or (+) PCR at baseline.

- **The secondary endpoints are:**

- Numbers and percentages (with 95% CI) of subjects with MAAEs, AESI, or SAE through the EOS by MedDRA classification, severity score, and relatedness in medically stable HIV-positive adult subjects regardless of baseline serostatus and stratified by baseline serostatus.
- Serum IgG antibody levels specific for the SARS-CoV-2 rS protein antigen(s) as detected by ELISA using GMT OR SCR at Day 21 (post first dose), Day 35 (post second dose), and across later study time points in serologically naïve (to SARS-CoV-2) medically stable HIV-positive adult subjects. Derived/calculated endpoints based on these data will include GMEUs, GMFR, and SCR.

SCR is defined as the percentage of subjects with a post-vaccination titer \geq 4-fold over naïve background and \geq 2-fold over pre-existing titer.

Positive baseline status (+/-) using GMT and/or (+) PCR at baseline.

- Serum IgG antibody levels specific for the SARS-CoV-2 rS protein antigen as detected by ELISA, described across study time points with derived/calculated endpoints to include GMEUs, GMFR, and SCR in medically stable HIV-positive adult subjects stratified by baseline serostatus.
- Epitope-specific immune responses to the SARS-CoV-2 rS protein receptor binding domain measured by serum titers in an ACE2 receptor binding inhibition assay to include GMT or concentration, GMFR, SCR, and SRR in medically stable HIV-positive adult subjects stratified by baseline serostatus. SRR is defined as the proportion of subjects with rises in ELISA units exceeding the 95th percentile of placebo subjects at the same time point and based on prior SARS-CoV-2 exposure.
- Neutralizing antibody activity at Day 35 and across later study time points relative to baseline in a subset of serologically naïve (to SARS-CoV-2) medically stable HIV-positive adult subjects by absolute titers and change from baseline, including SCR (\geq 4-fold change) and SRR. Analysis to be stratified by baseline serostatus to investigate whether baseline status (+/-) impacts response.
- Counts and proportions of virologically confirmed, mild, moderate, and severe COVID-19 outcomes in serologically naïve (to SARS-CoV-2) medically stable HIV-positive adult subjects as previously described in the second primary efficacy endpoint for Cohort 1 (HIV-negative subjects).
- Incidence, maximum severity score, and symptom duration of SARS-CoV-2 infection by classification of symptomatic virologically confirmed, mild, moderate, and severe COVID-19 in serologically naïve (to SARS-CoV-2) medically stable HIV-positive adult subjects. Should COVID-19 illness scoring be substantially validated at the time of study start, application of the standard scoring may be applied.

- **Exploratory endpoints are:**

- As previously described in the first and second primary efficacy endpoints for Cohort 1 (HIV-negative subjects) in medically stable HIV-positive adult subjects but applied to baseline seronegative and seropositive (to SARS-CoV-2) subjects, combined and separately, and following the first or second dose.
- Serum IgG antibody, ACE2 receptor inhibition binding antibody, and neutralizing antibody specific for the SARS-CoV-2 virus or rS protein, described across study time points with derived/calculated endpoints to include GMEUs/titers, GMFR, and SCR at Day 21 (post first dose), Day 35 (post second dose), and across later study time points in HIV-positive and/or HIV-negative subjects, stratified by baseline serostatus; CD4+ counts and/or viral load in HIV-positive subjects.
- One or more SARS-CoV-2 viral antigen-specific immune responses (eg, anti-N antibodies) measured by serum titers/units in an appropriate assay to indicate an interval seroconversion at a given post-vaccination study time point. Descriptive measures will include GMT or concentration, GMFR, SCR, and SRR. SRR is defined as the proportion of subjects with rises in antibody units/titers exceeding the 95th percentile of placebo subjects at the same time point and based on prior baseline exposure.

STUDY DESIGN:

This is a Phase 2a/b, randomized, observer-blinded, placebo-controlled study to evaluate the efficacy, safety, and immunogenicity of SARS-CoV-2 rS with Matrix-M1 adjuvant in healthy HIV-negative adult subjects (Cohort 1 – HIV-negative). This study will also evaluate the safety and immunogenicity of SARS-CoV-2 rS with Matrix-M1 adjuvant in medically stable HIV-positive adult subjects (Cohort 2 – HIV-positive). The study will be conducted at anticipated high COVID-19 transmission areas in South Africa expected to occur from July 2020 and onwards during the Southern Hemisphere winter and beyond.

After signing the informed consent form, subjects may be screened within a window of up to approximately 45 days. In addition, subjects must have a screening qualitative PCR for SARS-CoV-2 performed with a negative test result within 5 days prior to Day 0 vaccination in order to exclude subjects with active SARS-CoV-2 infection at the time of initial vaccination. Subjects will be asked to provide consent for the use of samples for future testing or assay development specific to SARS-CoV-2 (or related variants).

Blood samples for HIV testing of presumptive HIV-negative subjects will be collected at screening for inclusion for randomization. HIV-positive subjects will have CD4+ and HIV-1 viral load assessments to confirm that subjects do not have moderate or severe immunosuppression on treatment (see eligibility criteria); blood samples for other serology (hepatitis B and hepatitis C) will be collected at baseline but will not be used for inclusion/exclusion for randomization as a medical history will suffice; however, individuals with positive serologies (hepatitis B or hepatitis C) will not be included in the primary and secondary immunogenicity analyses. Subjects testing negative or positive for COVID-19 antibodies at baseline will have immune responses assessed/reported separately, unless otherwise specified. All screening laboratory testing will be performed at one or more central contract laboratories using common testing methodology. Safety bloods will not be collected.

A minimum of approximately 3,200 to a maximum of approximately 4,404 male and female adult subjects aged ≥ 18 to < 85 years comprising a minimum of approximately 2,960 to a maximum of approximately 4,164 healthy HIV-negative adult subjects aged ≥ 18 to < 85 years (Cohort 1 – HIV-negative) and approximately 240 medically stable HIV-positive adult subjects aged ≥ 18 to < 65 years (Cohort 2 – HIV-positive) is planned for the study. For Cohort 1, an effort will be made to enrol a target of 10-25% of subjects who are ≥ 65 years of age. Within each cohort, subjects will be randomized in a 1:1 ratio via block randomization to receive up to 2 intramuscular (IM) injections of study vaccine (SARS-CoV-2 rS with Matrix-M1 adjuvant or placebo) as described in [Table S1-3](#).

Cohort 1 (HIV-negative) will commence enrolment first, with vaccination starting following, and contingent on, determination of an adequate safety profile of SARS-CoV-2 rS with Matrix-M1 adjuvant through Day 35 (ie, 14 days post-second dose) in the ongoing Phase 1 portion of Protocol 2019nCoV-101 (Australia) by the global Safety Monitoring Committee (SMC) that is anticipated to be available by late July/early August 2020. Enrolment and vaccination in each cohort will be staged for the purpose of safety.

- In Cohort 1 (HIV-negative), the first 888 subjects aged ≥ 18 to < 65 years (Stage 1) will be vaccinated and followed for at least 7 days after the first dose of study vaccine (Day 7). The global SMC will review unblinded safety/reactogenicity data through Day 7 to assess prespecified vaccination pause rules to allow commencement of vaccination in the remaining subjects aged ≥ 18 to < 85 years (Stage 2) of Cohort 1 (HIV-negative) and to commence concurrent vaccination of the first 80 subjects (Stage 1) of Cohort 2 (HIV-positive). NOTE: subjects aged ≥ 65 to < 85 years will only be enrolled during Stage 2 of Cohort 1.
- In Cohort 2 (HIV-positive), the first 80 subjects (Stage 1) will be vaccinated and followed for at least 7 days after the first dose of study vaccine (Day 7). The global SMC will review unblinded safety/reactogenicity data through Day 7 to assess prespecified vaccination pause rules to allow commencement of vaccination in the remaining 160 subjects (Stage 2) of Cohort 2 (HIV-positive).

Table S1-3 Study Vaccine Groups with Maximized Immunization Plan (Based on Phase 1/2 Data)

Cohorts/ Study Vaccine Groups	Number of Randomized Subjects	Up to 2 Vaccinations		
		Day 0		Day 21
		Stage 1 ^a	Stage 2 ^a	(+ 7 days)
Cohort 1: HIV-negative subjects				
SARS-CoV-2 rS (5 µg) + Matrix-M1 adjuvant (50 µg)	N = 1480-2082 ^b	444	1036-1638	1480-1638
Placebo	N = 1480-2082 ^b	444	1036-1638	1480-1638
Cohort 2: HIV-positive subjects				
SARS-CoV-2 rS (5 µg) + Matrix-M1 adjuvant (50 µg)	N = 120	40 ^c	80	120
Placebo	N = 120	40 ^c	80	120

Abbreviations: HIV = human immunodeficiency virus; SMC = Safety Monitoring Committee; US = United States.

- ^a Vaccination of each cohort will be divided into 2 stages for purposes of safety. Stage 1 of each cohort will first vaccinate approximately 888 subjects aged 18 to < 65 years. The SMC will review safety data through Day 7 in Stage 1 of Cohort 1 to determine progression to Stage 2 of Cohort 1, which will vaccinate the remaining subjects aged 18 to < 85 years in Cohort 1. NOTE: subjects aged ≥ 65 to < 85 years will only be enrolled during Stage 2 of Cohort 1.
- ^b A maximum of approximately 2,082 subjects per vaccine group in Cohort 1 may be enrolled (ie, up to a total of 4,164 subjects in Cohort 1).
- ^c Stage 1 enrolment for Cohort 2 will begin concurrently with Stage 2 enrolment of Cohort 1.

The study will consist of a screening period (Days –45 to 0); vaccination days (up to 2; Days 0 and 21); outpatient study visits on Days 0, 21 (+ 7 days), and 35 (+ 7 days); at 3 and 6 months (± 15 days) after the last vaccination; and an EOS telephone call at 12 months (± 15 days) after the last vaccination. The duration of the study, excluding screening, is approximately 12 months after the last vaccination (386 days for 2 vaccinations). At the completion of the study, subjects receiving placebo will have the option of receiving SARS-CoV-2 rS with Matrix-M1 adjuvant if acceptable safety and vaccine efficacy (VE) have been demonstrated.

A global SMC was convened to oversee the safety of the ongoing Phase 1/2 study (Protocol 2019nCoV-101) and will oversee one or more additional studies across the SARS-CoV-2 rS vaccine program. The global SMC will be asked to provide oversight for the current study. A senior South African scientist will be asked to join the global SMC for purposes of oversight of this study. A separate SMC may be convened for this study in case the global SMC is unavailable. In either case, the designated SMC will monitor the safety of subjects in the study and will follow an SMC charter. The SMC will review unblinded safety and reactogenicity data through Day 7 of Stage 1 of each cohort to assess vaccination pause rules to allow advancement from Stage 1 vaccination to Stage 2 vaccination as previously described. The SMC will convene to perform safety reviews on a scheduled basis; for immediate concerns regarding safety observations during this study; and as needed.

Due to the ongoing pandemic, recent national regulatory and local Institutional Review Board and public health guidance will be applied at the site locations regarding alternations in the ability of study subjects to attend an investigational site for protocol-specified visits, with the site’s investigator being allowed to conduct safety assessments (eg, telephone

contact, alternative location for assessment, including local laboratories or imaging centers) when necessary and feasible, as long as such visits are sufficient to assure the safety of study subjects. Serum samples may be drawn using local phlebotomy services, home health, or other modalities if 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 clinical site depending on the pandemic situation (eg, home vaccinations).

Vaccination Pause Rules:

Vaccination pause rules based on reactogenicity, AEs, and SAEs related to study participation will be in place to monitor subject safety during the study and govern advancement from Stage 1 to Stage 2 vaccination in each cohort based on assessment by the SMC.

AEs meeting any one of the following criteria will result in a hold being placed on subsequent vaccinations pending further review by the SMC and the sponsor:

- The occurrence of 2 or more related SAEs (final assessment by the sponsor per United States Food and Drug Administration Center for Biologics Evaluation and Research Guidance) in a given MedDRA system organ class within the first 7 days (Day 7) following Stage 1 vaccination in each cohort.
- Any toxicity grade 3 (severe) solicited (local or systemic) single AE term occurring in $\geq 10\%$ of subjects in the SARS-CoV-2 rS group within the first 7 days (Day 7) following Stage 1 vaccination in each cohort.
- Any grade 3 (severe) unsolicited single AE preferred term for which the investigator assesses as related that occurs in $\geq 5\%$ of subjects in the SARS-CoV-2 rS group, within the first 7 days (Day 7) following Stage 1 vaccination in each cohort.

The sponsor, along with medical monitor, may request an SMC review for any safety concerns that may arise in the study, even if they are not associated with any specific pause rule.

STUDY POPULATION:

Inclusion Criteria:

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

1. Adult male or female aged ≥ 18 to < 65 years at screening for Cohorts 1 and 2, and adult male or female aged ≥ 65 to < 85 years at screening for Cohort 1 only.
2. The subject has a body mass index of 17 to 40 kg/m², inclusive, at screening.
3. Willing and able to give informed consent prior to study enrolment and comply with study procedures, including potential home visits for COVID-19 follow-up.
4. Female subjects of childbearing potential (defined as any female 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 or documented plasma follicle-stimulating hormone level ≥ 40 mIU/mL]) must agree to be heterosexually inactive from at least 21 days prior to enrolment and through 6 months after the last vaccination OR agree to consistently

use any of the following methods of contraception from at least 21 days prior to enrolment and through 6 months after the last vaccination:

- a. Condoms (male or female) with spermicide (if acceptable in country)
- b. Diaphragm with spermicide
- c. Cervical cap with spermicide
- d. Intrauterine device
- e. Oral or patch contraceptives
- f. Norplant[®], Depo-Provera[®], or other in country regulatory-approved contraceptive method that is designed to protect against pregnancy
- g. Abstinence, as a form of contraception, is acceptable if in line with the subject's lifestyle

NOTE: Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. These procedures and laboratory test results must be confirmed by physical examination, by subject recall of specific date and hospital/facility of procedure, or by medical documentation of said procedure.

HIV-negative subjects only (Cohort 1):

5. Documentation of HIV-negative test result by HIV test assay approved in South Africa and performed at a central laboratory.
6. Healthy at screening. Healthy status will be determined by the investigator based on medical history, vital sign measurements, and physical examination at screening.

HIV-positive subjects only (Cohort 2):

7. Receiving highly active antiretroviral therapy (HAART) and he/she has been using the same regimen within at least 8 weeks before screening. Changes in antiretroviral dosage within 8 weeks prior to entering the study are permitted. In addition, the exchange of pharmacological formulation (eg, the conventional formulation for combination formulations) is allowed.
8. Medically stable at screening, as determined by the investigator (based on review of health status, vital signs, medical history, and targeted physical examination). Vital signs must be within normal ranges prior to the first vaccination. Subjects must have been completely **free of opportunistic infections in the 1 year prior to the first study vaccination** (opportunistic infections include but are not limited to: active pulmonary or extrapulmonary tuberculosis; candidiasis of bronchi, trachea, esophagus, or lungs; invasive cervical cancer; coccidioidomycosis; cryptococcosis; chronic intestinal cryptosporidiosis; cytomegalovirus diseases; HIV-related encephalopathy; herpes simplex related-chronic ulcers (>1 month duration), bronchitis, pneumonitis, or esophagitis; histoplasmosis; chronic intestinal isosporiasis; Kaposi's sarcoma; lymphoma; Mycobacterium avium complex or Mycobacterium kansasii or other Mycobacterium; Pneumocystis carinii pneumonia;

- recurrent pneumonia, progressive multifocal leukoencephalopathy; Salmonella septicemia; toxoplasmosis of brain; or wasting syndrome due to HIV).
9. Have a HIV-1 viral load < 1000 copies/mL within 45 days of randomization.
 10. Documentation of HIV-positive test result by HIV test assay approved in South Africa and performed at a central laboratory.

Exclusion Criteria:

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

1. Any ongoing, symptomatic acute illness requiring medical or surgical care or chronic illness (excluding HIV in HIV-positive subjects) that required changes in medication in the past 2 months indicating that chronic illness/disease is not stable (at the discretion of the investigator). This includes any current workup of undiagnosed illness that could lead to a new condition.
2. Chronic disease inclusive of:
 - a. Hypertension (elevated blood pressure [BP]) \geq grade 2 (systolic BP \geq 160 mmHg; and/or diastolic BP \geq 100 mmHg) according to the South African Hypertension Society's Practice Guidelines [Seedat 2014; Rayner 2019];
NOTE: Hypertension [elevated BP] \leq grade 1 (systolic BP \leq 159 mmHg; diastolic BP \leq 99 mmHg) according to the South African Hypertension Society's Practice Guidelines is NOT exclusionary [Seedat 2014; Rayner 2019].
 - b. Congestive heart failure with a history of an acute exacerbation of any severity in the prior 2 years;
 - c. Chronic obstructive pulmonary disease (COPD) with a history of an acute exacerbation of any severity in the prior 2 years;
 - d. In the past 3 months, evidence of unstable coronary artery disease as manifested by cardiac interventions (eg, cardiac stent placement, coronary artery bypass graft surgery [CABG]), new cardiac medications for control of symptoms, or unstable angina;
NOTE: Stable coronary heart disease is NOT exclusionary.
 - e. Asthma requiring regular/chronic control medication (eg, short-acting beta2-agonist [SABA] > 2 days per week; or any chronic use of inhaled corticosteroids [ICS], long-acting beta2-agonist [LABA], leukotriene receptor antagonist [LTRA], or oral corticosteroids), and/or worsening of asthma symptoms in the past 3 months;
NOTE: Asthma not requiring regular/chronic control medication, and not requiring SABA > 2 days per week, and not demonstrating worsening of symptoms in the past 3 months, will NOT be excluded.
 - f. Type 1 or type 2 diabetes (adult onset) requiring insulin;
NOTE: Non-insulin dependent type 2 diabetes is NOT exclusionary.

- g. Chronic kidney disease/renal insufficiency;
- h. Chronic gastrointestinal and hepatic diseases; or
- i. Chronic neurological diseases (such as multiple sclerosis, dementia, transient ischemic attacks, Parkinson's disease, degenerative neurological conditions, neuropathy, or epilepsy), history of stroke within 12 months with residual symptoms, or previous neurological disorder within 12 months with residual symptoms;

NOTE: History of migraine or chronic headaches or nerve root compression that have been stable on treatment for the last 4 weeks are NOT exclusionary.

- 3. Participation in research involving an investigational product (drug/biologic/device) within 45 days prior to first study vaccination.
- 4. Prior receipt of investigational or approved COVID-19 vaccine at any time.
- 5. History of a diagnosis of suspected or confirmed of COVID-19.
- 6. Received influenza vaccination within 14 days prior to first study vaccination, or any other vaccine within 4 weeks prior to first study vaccination, or planned vaccination within 5 weeks after study first study vaccination.
- 7. Any autoimmune or immunodeficiency disease/condition (iatrogenic or congenital), excluding HIV in HIV-positive subjects.

NOTE: Stable endocrine disorders that have a confirmed autoimmune etiology (eg, thyroid, pancreatic), including stable diabetes not requiring insulin are allowed.

- 8. Chronic administration (defined as more than 14 continuous days) of immunosuppressant, systemic glucocorticosteroids, or other immune-modifying drugs within 90 days prior to first study vaccination, excluding HAART in HIV-positive subjects.

NOTE: An immunosuppressant dose of glucocorticoid is defined as a systemic dose ≥ 10 mg of prednisone per day or equivalent. The use of topical, inhaled, and nasal glucocorticoids will be permitted.

- 9. Received immunoglobulin, blood-derived products, or other immunosuppressant drugs within 90 days prior to first study vaccination, excluding HAART in HIV-positive subjects.
- 10. Acute respiratory and/or non-respiratory illness consistent with potential COVID-19 (see [Table S1-2](#) for list of symptoms) concurrent or within 14 days prior to first study vaccination (medical history and/or physical examination) or documented temperature of $> 38^{\circ}\text{C}$ during this period.

NOTE: This is a temporary exclusion for which the subject may be re-evaluated if they remain free from acute respiratory and/or non-respiratory illness consistent with potential COVID-19 after 14 days. Should a subject have a SARS-CoV-2 positive test, they may NOT be randomized.

11. Known disturbance of coagulation (iatrogenic or congenital).

NOTE: The use of low-dose aspirin (≤ 325 mg/day) as prophylaxis is acceptable in dosages consistent with local standards of care, but the use of other platelet aggregation inhibitors, thrombin inhibitors, Factor Xa inhibitors, or warfarin derivatives is exclusionary, regardless of bleeding history, because these imply treatment or prophylaxis of known cardiac or vascular disease.

12. Active cancer (malignancy) within 3 years prior to first study vaccination (with the exception of adequately treated non-melanomatous skin carcinoma, at the discretion of the investigator).

13. Any known allergies to products contained in the investigational product or latex allergy or any history of anaphylaxis in relation to any previous vaccination.

14. Women who are breastfeeding or who are pregnant at the time of screening or plan to become pregnant within the first 6 months of the study.

15. History of alcohol abuse or drug addiction within 2 years prior to the first study vaccination.

16. Any condition (other than HIV in HIV-positive subjects) that, in the opinion of the investigator, would pose a health risk to the subject if enrolled or could interfere with evaluation of the study vaccine or interpretation of study results (including neurologic or psychiatric conditions deemed likely to impair the quality of safety reporting).

17. Study team member or first-degree relative of any study team member (inclusive of sponsor, and site personnel involved in the study).

Other Considerations:

Subjects meeting any of the following criteria may be delayed for subsequent vaccination:

- Respiratory symptoms in the past 3 days (ie, temperature of $> 38^{\circ}\text{C}$, cough, sore throat, difficulty breathing). Subject may be vaccinated once all symptoms have been resolved for > 3 days, although should have tested negative for COVID-19. Out of window vaccination is allowed for this reason.
- Any acute illness (eg, gastroenteritis, migraine, urinary tract infection, injury) that is causing symptoms that could, in the opinion of the investigator, impact the assessment of reactogenicity. Subject may be vaccinated once symptoms have resolved or are stabilized for > 3 days. Out of window vaccination is allowed for this reason.
- The following therapies are prohibited:
 - Routine (ie, non-emergent) vaccinations will NOT be allowed within 2 weeks of first study vaccination until 28 days after second study vaccination (Day 49).
 - No chronic administration (defined as more than 14 continuous days) of any immunosuppressant medication within 3 months of first study vaccination until the last study visit (except topical, inhaled, and nasal steroids; or short-term oral steroids [course lasting ≤ 14 days]). The use of topical, inhaled, and nasal

glucocorticoids will be permitted if other chronic disease conditions are not exclusionary.

- No continuous use of anticoagulants, such as coumarins and related anticoagulants (ie, warfarin) or novel oral anticoagulants/anti-platelet agents. Use of ≤ 325 mg of aspirin per day as prophylaxis is permitted.

NOTE: Routine medical standards of care are permitted, including vaccines needed for emergent indications (eg, tetanus booster in response to a penetrating injury).

- Subjects having any symptoms or signs of suspected COVID-19 infection (Table S1-2) that may also be due to post-vaccination reactogenicity within 7 days of **Day 0** study vaccine dose (ie, Days 0-6 following the first dose) will NOT be required to be tested for SARS-CoV-2 PCR. However, subjects having any symptoms or signs of suspected COVID-19 infection (Table S1-2) that may also be due to post-vaccination reactogenicity within 7 days of **Day 21** study vaccine dose (ie, Days 21-27 following the second dose) will be required to be tested for SARS-CoV-2 PCR according to COVID-19 standard surveillance procedures.
- Any subject with a new positive PCR-confirmed SARS-CoV-2 infection occurring from Day 0 and prior to second study vaccination will not be removed from the study and should receive the second study vaccination but must meet health requirements before receiving the second study vaccination (see first 2 bullets in this section).

STUDY VACCINES:

Study vaccinations (SARS-CoV-2 rS with Matrix-M1 adjuvant or placebo) will comprise up to 2 IM injections (Day 0 and Day 21), ideally in alternating deltoids, with the study vaccine assigned in a full dose injection volume of approximately 0.5 mL. For both Cohort 1 (HIV-negative) and Cohort 2 (HIV-positive), the dose level will be 5 μ g SARS-CoV-2 rS with 50 μ g Matrix-M1 adjuvant (mixed in clinic or previously co-formulated). All vaccinations will be administered on an outpatient basis by designated site personnel in a way to maintain the blind. Any pharmacy preparation with unblinded product will require unblinded site personnel who will not otherwise be involved in the study procedures or observation of subjects.

The dose/immunization schedule to be implemented in this study is based on the totality of nonclinical data accumulated to date for SARS-CoV-2 rS with Matrix-M1 adjuvant from several animal species, including protection in severe disease mouse and nonhuman primate challenge models [Tian 2020, Guebre-Xabier 2020], immunogenicity data in mice and nonhuman primates [Tian 2020, Guebre-Xabier 2020], and data from the first clinical study of SARS-CoV-2 rS nanoparticle vaccine (Study 2019nCoV-101) [Keech 2020], as well as nonclinical and clinical data from several Novavax Matrix-M adjuvanted emerging infectious disease vaccine antigens produced using Novavax's platform nanoparticle technology in *Spodoptera frugiperda* insect cells. These data collectively suggest that a dose level of 5 μ g SARS-CoV-2 rS with 50 μ g Matrix-M1 adjuvant, administered in a 2-dose regimen 21 days apart, is likely to induce a strong neutralizing antibody response (Investigator's Brochure and Matrix-M safety supplement). Adaptive features will include the potential to expand the number of subjects enrolled into Cohort 1 (HIV-negative) based on the evolving national

COVID-19 epidemic and rates of clinically symptomatic cases, in order to accrue adequate numbers of endpoints to analyze one or both primary efficacy endpoints.

STUDY PROCEDURES:

Efficacy Assessments:

Nasal Swabs for Virus Detection:

Nasal swabs of the mid-turbinate and/or nasopharyngeal area for virus detection will be taken at each study visit described in the SOE (Table 3-2), and during COVID-19 Surveillance Visits (Initial and Follow-Up) triggered by symptoms of suspected COVID-19. This includes an additional screening visit within 5 days prior to study vaccination to exclude subjects recently infected with SARS-CoV-2.

Pulse Oximetry:

Blood oxygen saturation levels will be measured using a portable, study provided fingertip pulse oximeter (Massimo MightySat® Rx Fingertip Pulse Oximeter, or sponsor approved equivalent in case of unavailability) at the time points specified in the SOE (Table 3-2), both for study site-based or non-study site-based pulse oximetry assessments (eg, home-based or healthcare-based Surveillance Visit).

Active and Passive Surveillance for Suspected COVID-19:

Monitoring (active/passive surveillance) for COVID-19 endpoints will occur every 2 weeks from Day 8 through 01 December 2020 (or longer until the local epidemic is no longer deemed to be active in the judgement of the sponsor) and then every 4 weeks thereafter until EOS as described in the SOE (Table 3-2). If the national epidemic subsequently reintensifies, then more intensive active/passive surveillance may be reinstated. The InFLUenza Patient-Reported Outcome (FLU-PRO[®]) questionnaire will be used to monitor suspected COVID-19 episodes occurring throughout the study.

Beginning on Day 8, subjects will enter active and passive surveillance for suspected COVID-19. Surveillance will include provision of a Study Identification (ID) Card that provides details on study participation, study site contact information, and assessment of symptoms of suspected COVID-19 using the FLU-PRO questionnaire. The Study ID Card should be presented to healthcare providers not affiliated with the study who encounter subjects with symptoms of suspected COVID-19.

- **Active surveillance** (applicable from Day 8 through EOS)
 - Outbound calls will be made by site staff every 2 weeks from Day 8 post first vaccination to 01 December 2020 (or longer until the local epidemic is no longer deemed to be active in the judgement of the sponsor) and every 4 weeks thereafter until EOS to solicit symptoms of suspected COVID-19 using an approved script. Newly discovered symptoms of suspected COVID-19 will trigger a COVID-19 Surveillance Visit (Initial and Follow-Up) at the study site or at home for evaluation (as described in the COVID-19 Surveillance Visit). If a subject has recently had a COVID-19 Surveillance Visit, then the outbound call will serve as a follow-up to document whether symptoms of suspected COVID-19 have resolved or remain ongoing.
- **Passive surveillance** (applicable from Day 8 through EOS)
 - Instructions to subjects to contact the study site within 24 hours for symptoms of suspected COVID-19.
 - Weekly reminder text messages from Day 8 post first vaccination to 01 December 2020 (or longer until the local epidemic is no longer deemed to be active in the judgement of the sponsor) and every 2 weeks thereafter until EOS to remind subjects to call the study site if they develop symptoms of COVID-19 (see [Table S1-2](#) for list of symptoms).
 - Newly-discovered symptoms of suspected COVID-19 (see [Table S1-2](#) for list of symptoms) will trigger a COVID-19 Surveillance Visit (Initial and Follow-Up) at the study site or at home for evaluation (as described in COVID-19 Surveillance Visit).
 - If the initial evaluation of the symptoms of suspected COVID-19 is performed by a healthcare provider not affiliated with the study (eg, in an urgent care clinic, emergency room, outpatient clinic, ad hoc COVID-19 treatment facility, etc), he/she should notify the study staff of the subject's status as per the information provided on the Study ID Card. The study staff once notified will trigger a COVID-19 Surveillance Visit (Initial and Follow-Up).

Assessment of Symptoms of Suspected COVID-19:

Respiratory and non-respiratory symptoms consistent with suspected COVID-19 will be defined for all modes of surveillance by a self-reported new onset of:

- Active surveillance
 - Fever (defined by subjective or objective measure, regardless of use of anti-pyretic medications) **OR**
 - ≥ 2 COVID-19 respiratory/non-respiratory symptoms consistent with suspected COVID-19 (see [Table S1-2](#) for list of symptoms).
- Passive surveillance
 - Self-presentation for **any** respiratory/non-respiratory symptom consistent with suspected COVID-19 (see [Table S1-2](#) for list of symptoms).

EVERY episode of a “new onset” of symptoms of suspected COVID-19 will trigger a COVID-19 Surveillance Visit (Initial and Follow-Up) and will be assessed using the FLU-PRO questionnaire as described in the COVID-19 Surveillance Visit (Initial and Follow-Up).

“New onset” will require at least a preceding 7-day period free of symptoms, or with baseline symptoms, to differentiate an episode from any prior illness.

Severity of COVID-19 Symptoms:

COVID-19 symptoms will be categorized as virologically confirmed, mild, moderate, or severe as described in [Table S1-1](#).

COVID-19 Surveillance Visit (Initial and Follow-Up):

Procedures to occur during site or home COVID-19 Surveillance Visit (both Initial and Follow-Up) will be triggered by symptoms of suspected COVID-19 captured by active or passive surveillance.

When a subject is determined to have a new onset of **fever OR ≥ 2 COVID-19 respiratory/non-respiratory symptoms consistent with suspected COVID-19** on active surveillance **OR any COVID-19 respiratory/non-respiratory symptoms consistent with suspected COVID-19** on passive surveillance, the subject will immediately begin to assess the symptoms of suspected COVID-19 on a daily basis for 10 days using the FLU-PRO questionnaire, starting from the day of the new onset of symptoms and will be invited to return to the study clinic as soon as possible for an Initial COVID-19 Surveillance Visit (or will be seen by an outbound home visit by study staff depending on local conditions).

Initial COVID-19 Surveillance Visit

An Initial COVID-19 Surveillance Visit will be performed at the study site (or home) and will occur as soon as possible within approximately **1-3 days** of new symptom onset (however, data from specimens obtained up to 14 days will be accepted). The visit will consist of the following:

- Review and confirmation of the history of suspected COVID-19 symptoms, including approximate date of onset of illness and solicitation of each symptom (see [Table S1-2](#) for list of symptoms).
- Vital signs, including resting respiratory rate (on room air or the subject’s basal level of chronic supplemental oxygen use) and pulse oximetry (using MightySat® Rx Fingertip Pulse Oximeter), will be captured as numerical values. Lung auscultation (exam) will be performed by a study physician or nurse.
- Ascertainment of any unscheduled healthcare visit by the subject (or home visit by a healthcare provider) in response to symptoms of suspected COVID-19.
- Ascertainment of new concomitant medications (especially antibiotics) or altered doses/frequencies of existing concomitant medications resulting from symptoms of suspected COVID-19.
- Collection of a specimen of upper respiratory secretions via nasal mid-turbinate swab for qualitative PCR detection of SARS-CoV-2.

If a subject is unable to come to the study site for an Initial COVID-19 Surveillance Visit due to a hospitalization, the study site staff (study physician or nurse) will make every effort to visit the subject in the hospital to perform the Initial COVID-19 Surveillance Visit assessments (ie, review of symptom history, collection of nasal swab for PCR, measurement of vital signs including pulse oximetry, lung exam, and concomitant medications).

Follow-Up COVID-19 Surveillance Visit

A Follow-Up COVID-19 Surveillance Visit will occur approximately 4 (+2) days after the Initial COVID-19 Surveillance Visit to monitor for progression of disease. Every Initial COVID-19 Surveillance Visit must have a corresponding Follow-up Surveillance visit. This Follow-up COVID-19 Surveillance visit will consist of the following:

- If the nasal sample from the Initial COVID-19 Surveillance Visit tests **positive** for SARS-CoV-2 virus by qualitative PCR, the subject will NOT return to the study site for re-evaluation. Instead, the study staff will conduct the **Follow-Up COVID-19 Surveillance Visit at HOME** approximately 4 (+2) days after the Initial COVID-19 Surveillance Visit to ascertain worsening/progression of COVID-19 symptoms. This follow-up home visit by study staff (performed by a study physician or nurse) will include all of the same procedures outlined in this section, including review of symptom history, measurement of vital signs (including pulse oximetry), and lung auscultation; however, a repeat nasal mid-turbinate swab will not be obtained since the subject has already tested positive.
- If the nasal sample from the Initial COVID-19 Surveillance Visit tests **negative** for SARS-CoV-2 by qualitative PCR or the sample is inadequate for analysis, the subject will be **re-evaluated** in the clinic (or home) approximately 4 (+ 2) days after the Initial COVID-19 Surveillance Visit to ascertain worsening/progression of suspected COVID-19 symptoms AND to obtain a **second** nasal mid-turbinate swab for qualitative PCR detection of SARS-CoV-2. This re-evaluation will include all of the same procedures outlined in this section, including review of symptom history, measurement of vital signs (including pulse oximetry), and lung auscultation.

If a subject is unable to come to the study site for an Follow-up COVID-19 Surveillance Visit due to a hospitalization, the study site staff (study physician or nurse) will make every effort to visit the subject in the hospital to perform the Follow-up COVID-19 Surveillance Visit assessments (ie, review of symptom history, collection of nasal swab for PCR, measurement of vital signs including pulse oximetry, lung exam, and concomitant medications).

After the Follow-Up COVID-19 Surveillance Visit, subjects will continue to receive telephone contacts approximately **every week** for ascertainment of COVID-19 symptom status until resolution of symptoms. Subsequent calls will document resolution or return to baseline of COVID-19 symptoms in order to calculate illness duration (date of symptom onset to day of symptom resolution) and will collect any additional healthcare visits, hospitalizations, and/or concomitant medications due to the suspected COVID-19. Once symptoms resolve, telephone contacts for active surveillance will return to every 2 or 4 weeks depending on the required frequency of active surveillance at that point in the study.

EVERY episode of a “new onset” of symptoms of suspected COVID-19 will trigger a COVID-19 Surveillance Visit (Initial and Follow-Up) and subject completion of a FLU-PRO questionnaire for 10 days.

Should a subject visit an emergency room, be admitted to the hospital or a COVID-19 ward, and active/passive surveillance symptom-triggered nasal swab collection is missed, then the local public health COVID-19 diagnostic test (or COVID-19 diagnostic test performed in the healthcare setting) will be taken as a valid result.

Importantly, following any emergency visit or hospitalization episode for suspected COVID-19, clinical data on symptoms, vital signs, exam findings, COVID-19 and other diagnostic testing, diagnoses, and complications occurring during the suspected COVID-19 emergency room and/or hospitalization episode will be collected from available medical records on a study specific hospitalization/emergency room data collection form.

If the subject’s Day 0 swab tests positive by SARS-CoV-2 PCR, then the subject should (regardless of the initial presence or absence of COVID-19 symptoms): a) begin to complete the FLU-PRO questionnaire and b) receive a single HOME visit on Day 7 to complete BOTH the Follow-Up Surveillance Visit and the Day 7 Visit procedures. If a subject tests positive by SARS-CoV-2 PCR on a swab collected at a scheduled study visit (eg, Day 7, 21, 35; and at 3 and 6 months after the last vaccination), then the subject should (regardless of the initial presence or absence of COVID-19 symptoms): a) begin to complete the FLU-PRO questionnaire and b) receive a Follow-Up Surveillance Visit at HOME approximately 4 (+ 2) days later.

All surveillance nasal swab samples obtained via site staff collection will be sent to one or more designated central laboratories (eg, Clinical Laboratory Services [CLS]) using harmonized methods where a validated qualitative PCR test will be performed in near real time for detection of SARS-CoV-2.

Should a medical visit be warranted based on symptomatology and need for treatment (and allowed via local isolation guidance), such a visit may occur using telemedicine, home visitation, or clinic visit.

Subjects will be notified of positive SARS-CoV-2 results as soon as locally practicable due to requirements of self-isolation and potential transmission.

Key clinical endpoint definitions to be used are summarized below:

- **Primary infection** will be defined as the first (+) PCR regardless of symptoms in a previously seronegative subject.
- **Primary symptomatic infection** will be defined as the first (+) PCR with symptoms of COVID-19 during the previous 7 days.

Note that (+) PCR COVID-19 symptoms and events captured as efficacy endpoints will NOT be doubly recorded in the AE electronic case report form, unless a particular illness fulfils the definition of an SAE.

FLU-PRO:

The 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, disturbances in smell and taste) added that have been associated with COVID-19. In the current study, subjects will complete the FLU-PRO daily for 10 days at home starting from the day of the new onset of symptoms. A 10-day FLU-PRO questionnaire should be completed for every episode of new onset of suspected COVID-19 symptoms. Each question is brief (sign or symptom only with severity rating). The entire questionnaire takes under 4 minutes each day to complete. FLU-PRO scoring includes total and subscale scores for symptom severity by body system. The instrument also provides data on the presence/absence of symptoms, symptom profiles, and change over time.

Immunogenicity Assessments:

Blood samples for immunogenicity assessments will be collected before vaccination and at selected time points following vaccination ([Table 3-2](#)). Immune measurements (ELISA) will be conducted on serum (IgG) for SARS-CoV-2 rS protein antigen(s). Additional immunogenicity assessments specific to SARS-CoV-2 (or related variants) will include an ACE2 receptor binding inhibition assay and a neutralizing antibody assay. Serological assays may be performed to measure immune responses to 1 or more non-spike protein SARS-CoV-2 viral antigens in order to distinguish between serological responses to vaccine versus natural infection. Aliquots of all collected samples from this study may be retained for additional testing with antigens specific to SARS-CoV-2 (or related variants) for a maximum of 25 years (starting from the date at which the last subject had the last study visit), unless local rules, regulations, or guidelines require different timeframes or different procedures, in accord with subject consent.

Safety Assessments:

The timing and frequency of all safety assessments are listed in the SOE ([Table 3-2](#)). Safety assessments will include monitoring and recording of solicited (local and systemic reactogenicity events) and unsolicited AEs; MAAEs; AESI; SAEs; vital sign measurements; physical examination findings; and occurrence of SARS-CoV-2 infection as measured by nasal mid-turbinate swab and using qualitative PCR following subject-reported symptoms. COVID-19 severity will be categorized as virologically confirmed, mild, moderate, or severe according to protocol-specified criteria. Recording of solicited and unsolicited AEs may be conducted by electronic data capture/reporting. Potential immune-mediated medical conditions (PIMMC) and AESI specific to potential disease enhancement for COVID-19 will also be monitored (see [Section 9.4](#) [Appendix 4] for details).

STATISTICAL ANALYSIS PLANS:

Sample Size:

This study is designed to enroll a minimum of approximately 3,200 to a maximum of approximately 4,404 subjects divided among 2 cohorts as follows:

- Approximately 2,960 to 4,164 subjects aged ≥ 18 to < 85 years in Cohort 1 (HIV-negative) that include a minimum of approximately 1,480-2,082 subjects receiving SARS-CoV-2 rS with Matrix-M1 adjuvant.
- Approximately 240 subjects aged ≥ 18 to < 65 years in Cohort 2 (HIV-positive) that include a minimum of approximately 120 subjects receiving SARS-CoV-2 rS with Matrix-M1 adjuvant.

The target sample size of 1,480-2,082 actively-immunized subjects in Cohort 1 (HIV-negative) is sufficient to detect an AE rate of at least 1 in 625 subjects (ie, background rates of 0.16%) with 90% probability.

The target sample size of 120 actively-immunized subjects in Cohort 2 (HIV-positive) is sufficient to detect an AE rate of at least 1 in 53 subjects (ie, background rates of 1.9%) with 90% probability.

Power calculations were performed using the two-sided 97.5% CIs (ie, one-side alpha of 0.0125) to be conservative. Cohort 1 (HIV-negative) is designed to provide at least 80% power for each of the 2 independent primary endpoints based on the following assumptions ([Table S1-4](#)):

1. A symptomatic COVID-19 incident rate of 5% in the placebo group and a vaccine efficacy (VE) of 60%.
2. A symptomatic moderate or severe COVID-19 incident rate of 2.5% in the placebo group and a VE of 80%.
3. 90% evaluability rate for the per-protocol efficacy (PP-EFF) population (assuming 10% unevaluable due to attrition and/or baseline-seropositive subjects).

Table S1-4 Sample Size Needed for 80% Power

Independent Primary Endpoints ^a	Placebo Attack Rate	Vaccine Efficacy	LBCI Success Criteria	Enrolled Sample Size ^b		
				Per Group Size	Total Size	Number of Events
Any COVID-19 Symptoms	5%	30%	> 0%	3819	7638	292
	5%	40%		2027	4054	146
	5%	50%		1219	2438	82
	5%	60%		792	1584	50
	5%	70%		541	1082	32
	5%	80%		383	766	21
	4.5%	30%		4262	8524	293
	4.5%	40%		2261	4522	147
	4.5%	50%		1360	2720	83
	4.5%	60%		883	1766	50
	4.5%	70%		603	1206	32
	4.5%	80%		428	856	21
	4.0%	30%		4817	9634	295
	4.0%	40%		2554	5108	147
	4.0%	50%		1536	3072	83
	4.0%	60%		997	1994	50
	4.0%	70%		681	1362	32
	4.0%	80%		482	964	21
Moderate or Severe COVID-19 Symptoms	2.5%	50%	> 0%	2487	4974	84
	2.5%	60%		1613	3226	51
	2.5%	70%		1102	2204	32
	2.5%	80%		779	1558	21
	2.0%	50%		3120	6240	84
	2.0%	60%		2024	4048	51
	2.0%	70%		1382	2764	32
	2.0%	80%		978	1956	21

Abbreviation: CI = confidence interval; LBCI = lower bound of the confidence interval; PP-EFF = per-protocol efficacy.

^a Each endpoint to be tested at one-sided alpha of 0.0125 (ie, lower bound of two-sided 97.5% CI).

^b Accounting for 90% evaluability rate for the PP-EFF population.

Analysis Sets:

The intent-to-treat efficacy (ITT-EFF) and immunogenicity (ITT-IMM) analysis sets will include all subjects who are randomized and receive at least 1 dose study vaccine (SARS-CoV-2 rS with Matrix-M1 adjuvant or placebo), regardless of protocol violations or missing data. The intent-to-treat (ITT) analysis set will be used as a supportive analysis population for the immunogenicity and efficacy analyses and will be analyzed according to the study vaccine group as randomized.

The safety analysis set will include all subjects who receive at least 1 dose of study vaccine (SARS-CoV-2 rS with Matrix-M1 adjuvant or placebo). Subjects in the safety analysis set will be analyzed according to the vaccine actually received.

The PP-EFF will include seronegative subjects who receive both doses of study vaccine (SARS-CoV-2 rS with Matrix-M1 adjuvant or placebo) and have no major protocol deviations affecting the primary efficacy outcome as assessed by the sponsor prior to unblinding. All analyses of the PP-EFF population will exclude any illness episodes with positive SARS-CoV-2 by any validated PCR or antibody test occurring before 7 days after the second vaccine dose (eg, Day 28).

The per-protocol immunogenicity (PP-IMM) analysis set will include subjects who receive both doses of study vaccine (SARS-CoV-2 rS with Matrix-M1 adjuvant or placebo), have at least a baseline and 1 serum sample result available after vaccination, are negative for hepatitis B and C, and have no major protocol violations that are considered clinically relevant to impact immunogenicity response at the corresponding study visit as assessed by the sponsor prior to unblinding. For each visit, the SARS-CoV-2 unexposed population will exclude any illness episodes with positive SARS-CoV-2 by any validated PCR or antibody test prior to each visit. Prior-exposed subjects will be determined using baseline SARS-CoV-2 immunity defined as positive SARS-CoV-2 by qualitative PCR or serum IgG antibody at baseline, or positive SARS-CoV-2 by qualitative PCR through Day 21 or Day 35, according to the specified analysis. Analysis will be performed to assess if immune responses differ between exposed and unexposed individuals (ie, whether prior exposure alters dosing regimen considerations in a pandemic response).

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

Efficacy Analyses:

The 2 independent primary efficacy endpoints will be analyzed on the ITT-EFF and PP-EFF populations. Conclusions concerning declaration of attainment of the primary efficacy endpoint at the completion of the study will only be based on the PP-EFF population. In addition, supportive analyses based on the ITT-EFF population will also be performed.

The VE is defined as $VE (\%) = (1 - RR) \times 100$, where RR = relative risk of incidence rates between the 2 study vaccine groups (SARS-CoV-2 rS with Matrix-M1 adjuvant or placebo). The official (ie, event-driven) analysis for the primary objective in the PP-EFF population will be carried out at an overall one-sided Type I error rate of 0.025 for the 2 independent primary endpoints. Since the demonstration of the primary objective can be achieved if at least 1 of the 2 primary endpoints meets the prespecified success criteria, the statistical analysis will be performed in the following order:

1. Construct two-sided 95% CIs for the 2 primary efficacy endpoints. If both lower bounds are $> 0\%$, declare that both endpoints have met the success criteria. Otherwise, proceed to the next step.
2. Construct two-sided 97.5% CIs for the 2 primary efficacy endpoints. If the higher of the lower bounds is $> 0\%$, declare that only the endpoint associated with lower bound $> 0\%$ has met the success criterion. Otherwise, both primary efficacy endpoints did not meet the success criteria.

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 study 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 subject identifier. Poisson distribution will be used with a link function logarithm.

Hypothesis testing of either of the independent primary efficacy endpoints will be carried out against $H_0: VE \leq 0\%$. Rejection of the null hypothesis, $H_0: VE \leq 0\%$ demonstrates a statistically significant vaccine effect for either primary endpoint. The study will continue for the intended duration to measure immunogenicity and safety endpoints, regardless of a primary endpoint efficacy success. The official analysis of the primary efficacy endpoints will be triggered when at least 50 PP-EFF subjects with symptomatic mild, moderate, or severe COVID-19 or at least 21 PP-EFF subjects with symptomatic moderate or severe COVID-19 have accrued. Also, in order to be able to respond to the unexpected and rapidly evolving COVID-19 pandemic situation globally, other factors such as requests by government or public health agencies may also be factored into the decision-making to unblind the study for the official analysis, but this always occurs in consultation with lead regulatory agencies.

In order to address the uncertainty around the COVID-19 circulation in the study population, an active monitoring of the blinded endpoint accruals for the 2 independent primary efficacy endpoints will be performed by the sponsor. The sponsor may choose to switch 1 of the 2 primary efficacy endpoints to a secondary or exploratory efficacy endpoint prior to unblinding if it is determined that the accrual for the endpoint is likely to fall well short of the target number. The decision will be based solely on the total numbers of blinded endpoints accrued without consideration of vaccine group assignment. The decision will not be based on VE data. If this option is triggered, the remaining primary efficacy endpoint will be analyzed using one-sided Type I error rate of 0.025 (ie, two-sided 95% CI). The details for the criteria to be used to act on this option will be included in the SAP.

In addition to the official event-driven efficacy analysis, additional time-based efficacy analyses may be performed, including but not limited to through 6 and 12 months of follow-up (following last vaccination).

Immunogenicity Analyses:

The primary and secondary immunogenicity analyses will be performed using the PP-IMM and ITT-IMM analysis populations.

For the serum antibody levels measured by anti-spike IgG ELISA, ACE2 receptor binding inhibition assay, and microneutralization assays, the geometric mean at each study visit, the GMFR comparing to the baseline (Day 0) at each post-vaccination study visit, along with 95% CI will be summarized by study vaccine group. The 95% CI will be calculated based on the t-distribution of the log-transformed values for geometric means or GMFRs, then back transformed to the original scale for presentation. The SCR (proportion of subjects with ≥ 4 -fold rises if naïve at baseline and ≥ 2 -fold rise in ELISA units if SARS-CoV-2 exposed at baseline), and SRR (proportion of subjects with rises in ELISA units exceeding the 95th

percentile of placebo subjects at the same time point and based on prior SARS-CoV-2 exposure) along with 95% CIs based on the Clopper-Pearson method will be summarized by study vaccine group at each post-vaccination study visit.

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

Immunogenicity analysis of available data on 1 or more serological assays at Day 0 and 1 or more additional post-vaccination time points will be performed concurrently with the official endpoint-driven efficacy analysis, and at the end of the study; in addition, immunogenicity analysis may be performed on available data on 1 or more assays at selected Cohort Stages and/or time points, including but not limited to Days 0, 21, and 35 for Stage 1 of Cohort 1; and to Days 0, 21, 35, and 3 and 6 months after the last vaccination for both Cohorts.

Safety Analyses:

Numbers and percentages (with 95% CIs based on the Clopper-Pearson method) of subjects with solicited local and systemic AEs through 7 days after each vaccination will be summarized by study 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 study vaccine group.

Unsolicited AEs will be coded by preferred term and system organ class using the latest version of MedDRA and summarized by study vaccine group as well as by severity and relationship to study vaccine. AEs through 35 days after first vaccination; all MAAEs related to vaccine, SAE, or AESI through EOS will be listed separately and summarized by study vaccine group.

Vital sign measurements will be summarized by study vaccine group using descriptive statistics at baseline and following vaccination.

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

Safety analysis of available data through 1 or more post-vaccination time points will be performed concurrently with the official endpoint-driven efficacy analysis, and at the end of the study; in addition, safety analysis may be performed on available data on 1 or more Cohort Stages and/or time points, including but not limited to Days 0, 21, and 35 for Stage 1 of Cohort 1; and Days 0, 21, 35, and 3 and 6 months after the last vaccination for both Cohorts.

Planned Analyses Prior to Study Completion:

The SMC will be provided analysis data on an ongoing basis for confirming success and to review safety as the study progresses. The SMC Charter and the SAP will outline the sequential nature of these reviews.

1. INTRODUCTION

1.1 BACKGROUND

Novavax, Inc. is developing a recombinant vaccine adjuvanted with the saponin-based Matrix-M1™ for active immunization for the prevention of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The newly described coronavirus' genetic relationship with the 2002-2003 severe acute respiratory syndrome coronavirus (SARS-CoV) has resulted in adoption of the name SARS-CoV-2, with the associated disease being referred to COVID-19. SARS-CoV-2 recombinant spike (S) protein nanoparticle vaccine (SARS-CoV-2 rS) is constructed from the full-length, wild-type SARS-CoV-2 S glycoprotein based upon the GenBank gene sequence MN908947, nucleotides 21563-25384. 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* (Sf9) 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 been shown to enhance the immunogenicity of nanoparticle vaccines in nonclinical and clinical studies. Reference the current version of the Matrix-M adjuvant safety supplement to the SARS-CoV-2 rS Investigator's Brochure (IB) for additional details.

Further details on the study vaccine can be found in the SARS-CoV-2 rS IB.

1.2 RATIONALE FOR STUDY

The purpose of this study is 2-fold: 1) to evaluate the efficacy, safety, and immunogenicity of SARS-CoV-2 rS with Matrix-M1 adjuvant in serologically naïve (to SARS-CoV-2) healthy human immunodeficiency virus (HIV)-negative adult subjects (Cohort 1 – HIV-negative) and 2) to evaluate the safety and immunogenicity of SARS-CoV-2 rS with Matrix-M1 adjuvant in serologically naïve (to SARS-CoV-2) medically stable HIV-positive adult subjects (Cohort 2 – HIV-positive). The study will be conducted at anticipated high COVID-19 transmission areas in South Africa expected to occur from July 2020 and onwards during the Southern Hemisphere winter and beyond. The information provided in this study will inform progression of development efforts to take the vaccine forward in an emergency use authorization setting and/or for Phase 3 efficacy or effectiveness study(ies).

1.3 RATIONALE FOR DOSE SELECTION

The proposed dose level(s) of SARS-CoV-2 rS to be evaluated in this study is based on several data sources, including nonclinical and clinical studies with SARS-CoV-2 rS, as well as nonclinical and clinical studies with other Novavax, Inc. baculovirus-Sf9-produced nanoparticle vaccines including safety data in over 14,700 subjects from clinical studies with Ebolavirus glycoprotein (EBOV GP), respiratory syncytial virus fusion protein (RSV F), and

influenza vaccines. For details on nonclinical studies of SARS-CoV-2 rS and ongoing clinical studies with Novavax, Inc. baculovirus-Sf9-produced nanoparticle vaccines, please refer to the SARS-CoV-2 rS IB.

The proposed dose level of Matrix-M1 adjuvant to be evaluated in this study is based on the fully-analyzed human experience to date with Matrix-M adjuvants, which is confined to adults who have received 1- to 3-dose series of intramuscular (IM) doses of 25 to 75 µg. Further details regarding the Matrix-M adjuvant, including safety data from over 4,200 subjects in clinical studies with EBOV GP, RSV F, malaria, rabies, herpes simplex virus, and influenza vaccines with Matrix-M, are provided in the current version of the Matrix-M adjuvant safety supplement to the SARS-CoV-2 rS IB. It is anticipated that Matrix-M adjuvant will be required to provide a robust immunological response with appropriate humoral and cell-mediated immune pathway activation.

The dose/immunization schedule to be implemented in this study is based on the totality of nonclinical data accumulated to date for SARS-CoV-2 rS with Matrix-M1 from several animal species, including protection in severe disease mouse and nonhuman primate challenge models [Tian 2020, Guebre-Xabier 2020], immunogenicity data in mice and nonhuman primates [Tian 2020, Guebre-Xabier 2020], and data from the first clinical study of SARS-CoV-2 rS nanoparticle vaccine (Study 2019nCoV-101) [Keech 2020], as well as nonclinical and clinical data from several Novavax Matrix-M adjuvanted emerging infectious disease vaccine antigens produced using Novavax's platform nanoparticle technology in Sf9 insect cells.

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 designed to evaluate the immunogenicity and safety of SARS-CoV-2 rS nanoparticle vaccine with or without Matrix-M1 adjuvant in healthy subjects ≥ 18 to ≤ 59 years of age. Results of an interim analysis at Day 35 showed that SARS-CoV-2 rS with Matrix-M1 adjuvant was well tolerated and elicited robust immune responses [Keech 2020]. There were no serious adverse events (SAEs) or adverse events of special interest (AESI). 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 immunoglobulin G [IgG], human angiotensin-converting enzyme 2 [hACE2] receptor binding inhibition antibody, and neutralizing antibody) and was antigen dose-sparing, and the 2 dose 5µg 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 T helper 1 phenotype.

These data collectively suggest that a dose level of 5 µg SARS-CoV-2 rS with 50 µg Matrix-M1 adjuvant, administered in a 2-dose regimen 21 days apart, is likely to induce a strong neutralizing antibody response (IB and Matrix-M safety supplement). Adaptive features will include the potential to expand the number of subjects enrolled into Cohort 1 (HIV-negative)

based on the evolving national COVID-19 epidemic and rates of clinically symptomatic cases, in order to accrue adequate numbers of endpoints to analyze one or both primary efficacy endpoints.

All vaccinations will be administered on an outpatient basis by designated site personnel in a way to maintain the blind. Any pharmacy preparation with unblinded product will require unblinded site personnel who will not otherwise be involved in the study procedures or observation of subjects.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 STUDY OBJECTIVES

2.1.1 Cohort 1: HIV-Negative Subjects

The primary objectives are:

- To evaluate the efficacy of SARS-CoV-2 rS with Matrix-M1 adjuvant compared to placebo on the occurrence of symptomatic mild, moderate, or severe confirmed COVID-19 as demonstrated by qualitative polymerase chain reaction (PCR) in serologically naïve (to SARS-CoV-2) healthy HIV-negative adult subjects.
- To evaluate the efficacy of SARS-CoV-2 rS with Matrix-M1 adjuvant compared to placebo on the occurrence of symptomatic moderate or severe confirmed COVID-19 as demonstrated by qualitative PCR in serologically naïve (to SARS-CoV-2) healthy HIV-negative adult subjects.
- To accumulate and describe the safety experience for SARS-CoV-2 rS with Matrix-M1 adjuvant based on solicited short-term reactogenicity across a broad age spectrum (by toxicity grade) and by adverse event (AE) profile for vaccination through Day 35 in healthy HIV-negative adult subjects regardless of baseline serostatus and stratified by baseline serostatus.

The secondary objectives are:

- To evaluate the efficacy of SARS-CoV-2 rS with Matrix-M1 adjuvant compared to placebo on the occurrence of individual strata of symptomatic virologically confirmed, mild, moderate, or severe categories of confirmed COVID-19 as demonstrated by qualitative PCR in serologically naïve (to SARS-CoV-2) healthy HIV-negative adult subjects.
- To evaluate the efficacy of SARS-CoV-2 rS with Matrix-M1 adjuvant compared to placebo on the occurrence of hospitalization (regardless of severity) with confirmed COVID-19 as demonstrated by qualitative PCR in serologically naïve (to SARS-CoV-2) healthy HIV-negative adult subjects.

- To assess incidence, severity, and symptom duration of SARS-CoV-2 infection and to describe the characteristics of subjects with symptomatic virologically confirmed, mild, moderate, and/or severe COVID-19 in serologically naïve (to SARS-CoV-2) healthy HIV-negative adult subjects, overall and by age strata.
- To assess the immune response (IgG antibody to SARS-CoV-2 rS protein and ACE2 receptor binding inhibition) for SARS-CoV-2 rS with Matrix-M1 adjuvant at Day 21 (post first dose), Day 35 (post second dose), and across later study time points healthy HIV-negative adult subjects, regardless of baseline serostatus and stratified by baseline serostatus (to SARS-CoV-2).
- To describe the amplitude, kinetics, and durability of immune response in terms of enzyme-linked immunosorbent assay (ELISA) units of serum IgG antibodies and titers of ACE2 receptor binding inhibition to SARS-CoV-2 rS protein(s) at selected time points and relative to whether subjects had pre-existing antibodies to SARS-CoV-2, regardless of baseline serostatus and stratified by baseline serostatus (to SARS-CoV-2). To include reverse cumulative distribution curves.
- To describe the immune response to the primary 2-dose regimen of SARS-CoV-2 rS with Matrix-M1 adjuvant in terms of titers of neutralizing antibody at selected study time points in a subset of healthy HIV-negative adult subjects, regardless of baseline serostatus and stratified by baseline serostatus (to SARS-CoV-2).
- To assess overall safety through Day 35 for all AEs and through the end of study (EOS) for any medically attended adverse event (MAAE) attributed to vaccine, AESI, or SAE in healthy HIV-negative adult subjects regardless of baseline serostatus and stratified by baseline serostatus.

The exploratory objectives are:

- To evaluate the efficacy of SARS-CoV-2 rS with Matrix-M1 adjuvant compared to placebo on the occurrence of symptomatic virologically confirmed; symptomatic mild, moderate, or severe; OR symptomatic moderate or severe confirmed COVID-19 as demonstrated by qualitative PCR in healthy HIV-negative adult subjects, serologically naïve (to SARS-CoV-2) at **baseline and regardless of baseline serological status** to SARS-CoV-2, and following the **first or second dose** of study vaccine, overall and by age strata.
- To evaluate the efficacy of SARS-CoV-2 rS with Matrix-M1 adjuvant compared to placebo on the occurrence of serological evidence of SARS-CoV-2 infection as measured by a multiplex serological assay that measures the immune response to one or more non-vaccine SARS-CoV-2 viral antigens (eg, anti-nucleocapsid [anti-N] antibodies) at baseline and at selected time points (in order to distinguish between serological responses to vaccine versus natural infection). Responses to non-vaccine SARS-CoV-2 viral antigens will be described at selected time points. Note, responses to vaccine-related SARS-CoV-2 viral antigens (eg, spike protein and related epitopes)

reported on this multiplex serological assay may be described for qualitative purposes but will not be used to describe the primary or secondary immunogenicity endpoints.

2.1.2 Cohort 2: HIV-Positive Subjects

The primary objectives are:

- To accumulate and describe the safety experience for SARS-CoV-2 rS with Matrix-M1 adjuvant based on solicited short-term reactogenicity across a broad age spectrum (by toxicity grade) and by AE profile for vaccination through Day 35 in medically stable HIV-positive adult subjects regardless of baseline serostatus and stratified by baseline serostatus.
- To assess the immune response (IgG antibody to SARS-CoV-2 rS protein) for SARS-CoV-2 rS with Matrix-M1 adjuvant at Day 35 and whether baseline immune status (to SARS-CoV-2) has an impact in medically stable HIV-positive adult subjects (ie, regardless of baseline serostatus and stratified by baseline serostatus).

The secondary objectives are:

- To assess overall safety through Day 35 for all AEs and through the EOS for any MAAE attributed to vaccine, AESI, or SAE in medically stable HIV-positive adult subjects regardless of baseline serostatus and stratified by baseline serostatus.
- To assess the immune response (IgG antibody to SARS-CoV-2 rS protein and ACE2 receptor binding inhibition) for SARS-CoV-2 rS with Matrix-M1 adjuvant at Day 21 (post first dose), Day 35 (post second dose), and across later study time points in medically stable HIV-positive adult subjects, regardless of baseline serostatus and stratified by baseline serostatus (to SARS-CoV-2).
- To describe the amplitude, kinetics, and durability of immune response in terms of ELISA units of serum IgG antibodies and titers of ACE2 receptor binding inhibition to SARS-CoV-2 rS protein(s) at selected time points and relative to whether subjects had pre-existing antibodies to SARS-CoV-2 (ie, regardless of baseline serostatus and stratified by baseline serostatus). To include reverse cumulative distribution curves.
- To describe the immune response to the primary 2-dose regimen of SARS-CoV-2 rS with Matrix-M1 adjuvant in terms of titers of neutralizing antibody at selected study time points in a subset of medically stable HIV-positive adult subjects, regardless of baseline serostatus and stratified by baseline serostatus (to SARS-CoV-2).
- To describe the incidence of symptomatic virologically confirmed, mild, moderate, or severe confirmed COVID-19 as demonstrated by qualitative PCR in serologically naïve (to SARS-CoV-2) medically stable HIV-positive adult subjects.
- To describe the incidence of symptomatic moderate or severe confirmed COVID-19 as demonstrated by qualitative PCR in serologically naïve (to SARS-CoV-2) medically stable HIV-positive adult subjects.

- To assess severity and symptom duration of SARS-CoV-2 infection and to describe the characteristics of subjects with symptomatic virologically confirmed, mild, moderate, and/or severe COVID-19 in serologically naïve (to SARS-CoV-2) medically stable HIV-positive adult subjects.

The exploratory objectives are:

- To evaluate the efficacy of SARS-CoV-2 rS with Matrix-M1 adjuvant compared to placebo on the occurrence of symptomatic virologically confirmed; symptomatic mild, moderate, or severe; OR symptomatic moderate or severe COVID-19 as confirmed by qualitative PCR in medically stable HIV-positive adult subjects, serologically naïve (to SARS-CoV-2) at baseline and regardless of baseline serological status to SARS-CoV-2, and following the first or second dose of study vaccine.
- To describe the immune responses (IgG antibody, ACE2 receptor binding inhibition, and neutralizing antibody) to SARS-CoV-2 rS with Matrix-M1 adjuvant in HIV-positive subjects according to baseline levels of CD4+ counts and/or HIV viral load, at Day 35 and at selected study time points.
- To describe the immune responses (IgG antibody, ACE2 receptor binding inhibition, and neutralizing antibody) to SARS-CoV-2 rS with Matrix-M1 adjuvant in HIV-positive subjects relative to HIV-negative subjects at Day 35 and at selected study time points, regardless of baseline serostatus and stratified by baseline serostatus (to SARS-CoV-2).
- To evaluate the efficacy of SARS-CoV-2 rS with Matrix-M1 adjuvant compared to placebo on the occurrence of serological evidence of SARS-CoV-2 infection as measured by a multiplex serological assay that measures the immune response to one or more non-vaccine SARS-CoV-2 viral antigens (eg, anti-N antibodies) at baseline and at selected time points (in order to distinguish between serological responses to vaccine versus natural infection). Responses to non-vaccine SARS-CoV-2 viral antigens will be described at selected time points. Note, responses to vaccine-related SARS-CoV-2 viral antigens (eg, spike protein and related epitopes) reported on this multiplex serological assay may be described for qualitative purposes but will not be used to describe the primary or secondary immunogenicity endpoints.

2.2 STUDY ENDPOINTS

2.2.1 Cohort 1: HIV-Negative Subjects

The primary endpoints are:

Primary endpoints include 2 independent efficacy endpoints and a safety endpoint.

- FIRST PRIMARY EFFICACY ENDPOINT:** Positive (+) PCR-confirmed SARS-CoV-2 illness with **symptomatic mild, moderate, or severe COVID-19** (Table 2-1) in serologically naïve (to SARS-CoV-2) healthy HIV-negative adult subjects, with a lower bound confidence interval (CI) of > 0, from 7 days after the second vaccine dose (eg, Day 28) until the endpoint-driven efficacy analysis is triggered by the occurrence of a prespecified number of blinded endpoints across the 2 study vaccine arms and/or at prespecified time points.

Table 2-1: Endpoint Definitions of COVID-19 Severity

COVID-19 Severity	Endpoint Definitions
Virologically Confirmed	≥ 1 COVID-19 disease symptom in Table 2-2 AND Does not meet criteria for mild, moderate, or severe disease
Mild	≥ 1 of: <ul style="list-style-type: none"> Fever (defined by subjective or objective measure, regardless of use of anti-pyretic medications) New onset cough ≥ 2 COVID-19 respiratory/non-respiratory symptoms in Table 2-2 AND <ul style="list-style-type: none"> Does not meet criteria for moderate or severe
Moderate	≥ 1 of: <ul style="list-style-type: none"> Fever (defined by subjective or objective measure, regardless of use of anti-pyretic medications) + any 2 COVID-19 symptoms in Table 2-2 for ≥ 3 days (need not be contiguous days) High fever (≥ 38.4°C) for ≥ 3 days (need not be contiguous days) Any evidence of significant LRTI: <ul style="list-style-type: none"> Shortness of breath (or breathlessness or difficulty breathing) with or without exertion (greater than baseline) Tachypnea: 20 to 29 breaths per minute at rest SpO2: 94% to 95% on room air Abnormal chest x-ray or chest CT consistent with pneumonia or LRTI Adventitious sounds on lung auscultation (eg, crackles/rales, wheeze, rhonchi, pleural rub, stridor) AND <ul style="list-style-type: none"> Does not meet criteria for severe disease

Table 2-1: Endpoint Definitions of COVID-19 Severity

COVID-19 Severity	Endpoint Definitions
Severe	<p>≥ 1 of:</p> <ul style="list-style-type: none"> • Tachypnea: ≥ 30 breaths per minute at rest • Resting heart rate ≥ 125 beats per minute • SpO₂: ≤ 93% on room air or PAO₂/FiO₂ < 300 • High flow oxygen therapy or NIV/NIPPV (eg, CPAP or BiPAP) • Mechanical ventilation or ECMO • One or more major organ system dysfunction or failure (eg, cardiac/circulatory, pulmonary, renal, hepatic, and/or neurological, to be defined by diagnostic testing/clinical syndrome/ interventions), including any of the following: <ul style="list-style-type: none"> – ARDS – Acute renal failure – Acute hepatic failure – Acute right or left heart failure – Septic or cardiogenic shock (with shock defined as SBP < 90 mm Hg OR DBP < 60 mm Hg) – Acute stroke (ischemic or hemorrhagic) – Acute thrombotic event: AMI, DVT, PE – Requirement for: vasopressors, systemic corticosteroids, or hemodialysis. • Admission to an ICU • Death

Abbreviations: AMI = acute myocardial infarction; ARDS = acute respiratory distress syndrome; BiPAP = bi-level positive airway pressure; CPAP = continuous positive air pressure; CT = computed tomography; DBP = diastolic blood pressure; DVT = deep vein thrombosis; ECMO = extracorporeal membrane oxygenation; FiO₂ = fraction of inspired oxygen; ICU = intensive care unit; LRTI = lower respiratory tract infection; NIV = non-invasive ventilation; NIPPV = non-invasive positive pressure ventilation; PAO₂ = partial pressure of oxygen in the alveolus; PE = pulmonary embolism; SBP = systolic blood pressure; SpO₂ = oxygen saturation.

Symptomatic COVID-19 is defined as a self-reported acute respiratory/systemic new onset illness that is clinically consistent with COVID-19 based on the presence of fever (defined by subjective or objective measure, regardless of use of anti-pyretic medications) or ≥ 2 respiratory/non-respiratory tract symptoms (Table 2-2). In the case of rapid decompensation to a severe COVID-19 case, emergency department, hospital, or post-mortem data can be used for ascertainment of both clinical endpoint data, and for virologically confirmed positive cases without the initial presentation for case ascertainment and procuring a swab during a COVID-19 Surveillance Visit (Initial and Follow-Up).

Table 2-2: Symptoms of Suspected COVID-19

Respiratory	Non-Respiratory
New onset cough	Fever or feverishness (defined subjectively, or objective fever $\geq 37.8^{\circ}\text{C}$, regardless of use of anti-pyretic medications)
New onset rapid breathing	Myalgia (or muscle ache)
New onset shortness of breath (or breathlessness or difficulty breathing)	Chills
Sore throat	Loss of taste (or taste disturbance)
Loss of smell (or smell disturbance)	Headache
Nasal congestion	Diarrhea
Runny nose	Tiredness (or fatigue or weakness)
	Nausea or vomiting
	Loss of appetite

Abbreviations: COVID-19 = coronavirus disease 2019.

- SECOND PRIMARY EFFICACY ENDPOINT:** (+) PCR-confirmed SARS-CoV-2 illness with **symptomatic moderate or severe COVID-19** (Table 2-1) in serologically naïve (to SARS-CoV-2) healthy HIV-negative adult subjects, with a lower bound CI > 0 , from 7 days after the second vaccine dose (eg, Day 28) until the endpoint-driven efficacy analysis is triggered by the occurrence of a prespecified number of blinded endpoints across the 2 study vaccine arms and/or at prespecified time points.
- PRIMARY SAFETY ENDPOINTS:** Numbers and percentages (with 95% CIs) of subjects with solicited AEs (local, systemic) for 7 days following each vaccination (Days 0 and 21) by severity score, duration, and peak intensity in healthy HIV-negative adult subjects regardless of baseline serostatus and stratified by baseline serostatus. In the case of no toxicity, a score of zero (0) will be applied.

Numbers and percentages (with 95% CI) of subjects with unsolicited AEs (eg, treatment-emergent, serious, suspected unexpected serious, those of special interest, MAAEs) through Day 35 by Medical Dictionary for Regulatory Activities (MedDRA) classification, severity score, and relatedness in healthy HIV-negative adult subjects regardless of baseline serostatus and stratified by baseline serostatus.

The secondary endpoints are:

- (+) PCR-confirmed SARS-CoV-2 with COVID-19 in serologically naïve (to SARS-CoV-2) healthy HIV-negative adult subjects in terms of individual strata of symptomatic virologically confirmed, mild, moderate, or severe COVID-19 as previously described.
- (+) PCR-confirmed SARS-CoV-2 with COVID-19 in serologically naïve (to SARS-CoV-2) healthy HIV-negative adult subjects requiring hospitalization (regardless of severity).
- Incidence, maximum severity score, and symptom duration of SARS-CoV-2 infection by classification of symptomatic virologically confirmed, mild, moderate, and/or severe disease in serologically naïve (to SARS-CoV-2) healthy HIV-negative adult subjects, overall and by age strata. Should COVID-19 illness scoring be substantially validated at the time of study start, application of the standard scoring may be applied.
- Serum IgG antibody levels specific for the SARS-CoV-2 rS protein antigen(s) as detected by ELISA using geometric mean titers (GMT) OR seroconversion rate (SCR) at Day 21 (post first dose), Day 35 (post second dose), and across later study time points in healthy HIV-negative adult subjects, regardless of baseline serostatus and stratified by baseline serostatus (to SARS-CoV-2). Derived/calculated endpoints based on these data will include geometric mean ELISA units (GMEUs), geometric mean fold rise (GMFR), and SCR.

SCR is defined as the percentage of subjects with a post-vaccination titer \geq 4-fold over naïve background and \geq 2-fold over pre-existing titer.

Positive baseline status (+/-) using GMT and/or (+) PCR at baseline.

- Serum IgG antibody levels specific for the SARS-CoV-2 rS protein antigen as detected by ELISA, described across study time points with derived/calculated endpoints to include GMEUs, GMFR, and SCR in healthy HIV-negative adult subjects, regardless of baseline serostatus and stratified by baseline serostatus (to SARS-CoV-2).
- Epitope-specific immune responses to the SARS-CoV-2 rS protein receptor binding domain measured by serum titers in an ACE2 receptor binding inhibition assay, described across study time points, to include GMT, GMFR, SCR, and seroresponse rate (SRR) in healthy HIV-negative adult subjects, regardless of baseline serostatus and stratified by baseline serostatus (to SARS-CoV-2). SRR is defined as the proportion of subjects with rises in titers exceeding the 95th percentile of placebo subjects at the same time point and based on prior SARS-CoV-2 exposure.
- Neutralizing antibody activity at Day 35 and across later study time points relative to baseline in healthy HIV-negative adult subjects by absolute titers and change from baseline, including SCR (\geq 4-fold change) and SRR, regardless of baseline serostatus

and stratified by baseline serostatus (to SARS-CoV-2) to investigate whether baseline status (+/-) impacts response.

- Numbers and percentages (with 95% CI) of subjects with MAAEs, AESI, or SAE through the EOS by MedDRA classification, severity score, and relatedness in healthy HIV-negative adult subjects regardless of baseline serostatus and stratified by baseline serostatus.

The exploratory endpoints are:

- As previously described in the first and second primary efficacy endpoints for Cohort 1 (HIV-negative subjects) but applied to both baseline seronegative and seropositive (to SARS-CoV-2) subjects, combined and separately, and following the first or second dose, and by age strata.
- One or more non-vaccine SARS-CoV-2 viral antigen-specific immune responses (eg, anti-N antibodies) measured by serum titers/units in an appropriate assay to indicate an interval seroconversion at a given post-vaccination study time point. Descriptive measures will include GMT, GMFR, SCR, and SRR. SRR is defined as the proportion of subjects with rises in antibody units/titers exceeding the 95th percentile of placebo subjects at the same time point and based on prior baseline exposure.

2.2.2 Cohort 2: HIV-Positive Subjects

The primary endpoints are:

- Numbers and percentages (with 95% CIs) of subjects with solicited AEs (local, systemic) for 7 days following each vaccination (Days 0 and 21) by severity score, duration, and peak intensity in medically stable HIV-positive adult subjects regardless of baseline serostatus and stratified by baseline serostatus. In the case of no toxicity, a score of zero (0) will be applied.
- Numbers and percentages (with 95% CI) of subjects with unsolicited AEs (eg, treatment-emergent, serious, suspected unexpected serious, those of special interest, MAAEs) through Day 35 by MedDRA classification, severity score, and relatedness in medically stable HIV-positive adult subjects regardless of baseline serostatus and stratified by baseline serostatus.
- Serum IgG antibody levels specific for the SARS-CoV-2 rS protein antigen(s) as detected by ELISA using GMT OR SCR at Day 35 in medically stable HIV-positive adult subjects regardless of baseline serostatus and stratified by baseline serostatus. Derived/calculated endpoints based on these data will include GMEUs, GMFR, and SCR.

SCR is defined as the percentage of subjects with a post-vaccination titer ≥ 4 -fold over naïve background and ≥ 2 -fold over pre-existing titer.

Positive baseline status (+/-) using GMT and/or (+) PCR at baseline.

The secondary endpoints are:

- Numbers and percentages (with 95% CI) of subjects with MAAEs, AESI, or SAE through the EOS by MedDRA classification, severity score, and relatedness in medically stable HIV-positive adult subjects regardless of baseline serostatus and stratified by baseline serostatus.
- Serum IgG antibody levels specific for the SARS-CoV-2 rS protein antigen(s) as detected by ELISA using GMT OR SCR at Day 21 (post first dose), Day 35 (post second dose), and across later study time points in serologically naïve (to SARS-CoV-2) medically stable HIV-positive adult subjects. Derived/calculated endpoints based on these data will include GMEUs, GMFR, and SCR.

SCR is defined as the percentage of subjects with a post-vaccination titer \geq 4-fold over naïve background and \geq 2-fold over pre-existing titer.

Positive baseline status (+/-) using GMT and/or (+) PCR at baseline.

- Serum IgG antibody levels specific for the SARS-CoV-2 rS protein antigen as detected by ELISA, described across study time points with derived/calculated endpoints to include GMEUs, GMFR, and SCR in medically stable HIV-positive adult subjects stratified by baseline serostatus.
- Epitope-specific immune responses to the SARS-CoV-2 rS protein receptor binding domain measured by serum titers in an ACE2 receptor binding inhibition assay to include GMT, GMFR, SCR, and SRR in medically stable HIV-positive adult subjects stratified by baseline serostatus. SRR is defined as the proportion of subjects with rises in titers exceeding the 95th percentile of placebo subjects at the same time point and based on prior SARS-CoV-2 exposure.
- Neutralizing antibody activity at Day 35 and across later study time points relative to baseline in a subset of serologically naïve (to SARS-CoV-2) medically stable HIV-positive adult subjects by absolute titers and change from baseline, including SCR (\geq 4-fold change) and SRR. Analysis to be stratified by baseline serostatus to investigate whether baseline status (+/-) impacts response.
- Counts and proportions of symptomatic virologically confirmed, mild, moderate, and severe COVID-19 outcomes in serologically naïve (to SARS-CoV-2) medically stable HIV-positive adult subjects as previously described in the second primary efficacy endpoint for Cohort 1 (HIV-negative subjects).
- Incidence, maximum severity score, and symptom duration of SARS-CoV-2 infection by classification of symptomatic virologically confirmed, mild, moderate, and/or severe COVID-19 in serologically naïve (to SARS-CoV-2) medically stable HIV-positive adult subjects. Should COVID-19 illness scoring be substantially

validated at the time of study start, application of the standard scoring may be applied.

The exploratory endpoints are:

- As previously described in the first and second primary efficacy endpoints for Cohort 1 (HIV-negative subjects) in medically stable HIV-positive adult subjects but applied to baseline seronegative and seropositive (to SARS-CoV-2) subjects, combined and separately, and following the first or second dose.
- Serum IgG antibody, ACE2 receptor inhibition binding antibody, and neutralizing antibody specific for the SARS-CoV-2 virus or rS protein, described across study time points with derived/calculated endpoints to include GMEUs/titers, GMFR, and SCR at Day 21 (post first dose), Day 35 (post second dose), and across later study time points in HIV-positive and/or HIV-negative subjects, stratified by baseline serostatus; CD4+ counts and/or viral load in HIV-positive subjects.
- One or more SARS-CoV-2 viral antigen-specific immune responses (eg, anti-N antibodies) measured by serum titers/units in an appropriate assay to indicate an interval seroconversion at a given post-vaccination study time point. Descriptive measures will include GMT, GMFR, SCR, and SRR. SRR is defined as the proportion of subjects with rises in antibody units/titers exceeding the 95th percentile of placebo subjects at the same time point and based on prior baseline exposure.

3. STUDY DESIGN

This is a Phase 2a/b, randomized, observer-blinded, placebo-controlled study to evaluate the efficacy, safety, and immunogenicity of SARS-CoV-2 rS with Matrix-M1 adjuvant in healthy HIV-negative adult subjects (Cohort 1 – HIV-negative). This study will also evaluate the safety and immunogenicity of SARS-CoV-2 rS with Matrix-M1 adjuvant in medically stable HIV-positive adult subjects (Cohort 2 – HIV-positive). The study will be conducted at anticipated high COVID-19 transmission areas in South Africa expected to occur from July 2020 and onwards during the Southern Hemisphere winter and beyond.

After signing the informed consent form (ICF), subjects may be screened within a window of up to approximately 45 days. In addition, subjects must have a screening qualitative PCR for SARS-CoV-2 performed with a negative test result within 5 days prior to Day 0 vaccination in order to exclude subjects with active SARS-CoV-2 infection at the time of initial vaccination. Subjects will be asked to provide consent for the use of samples for future testing or assay development specific to SARS-CoV-2 (or related variants).

Blood samples for HIV testing of presumptive HIV-negative subjects will be collected at screening for inclusion for randomization. HIV-positive subjects will have CD4+ and HIV-1 viral load assessments to confirm that subjects do not have moderate or severe immunosuppression on treatment (see eligibility criteria); blood samples for other serology (hepatitis B and hepatitis C) will be collected at baseline but will not be used for

inclusion/exclusion for randomization as a medical history will suffice; however, individuals with positive serologies (hepatitis B or hepatitis C) will not be included in the primary and secondary immunogenicity analyses. Subjects testing negative or positive for COVID-19 antibodies at baseline will have immune responses assessed/reported separately, unless otherwise specified. All screening laboratory testing will be performed at one or more central contract laboratories using common testing methodology. Safety bloods will not be collected.

A minimum of approximately 3,200 to a maximum of approximately 4,404 male and female adult subjects aged ≥ 18 to < 85 years comprising a minimum of approximately 2,960 to a maximum of approximately 4,164 healthy HIV-negative adult subjects aged ≥ 18 to < 85 years (Cohort 1 – HIV-negative) and approximately 240 medically stable HIV-positive adult subjects aged ≥ 18 to < 65 years (Cohort 2 – HIV-positive) is planned for the study. For Cohort 1, an effort will be made to enrol a target of 10-25% of subjects who are ≥ 65 years of age. Within each cohort, subjects will be randomized in a 1:1 ratio via block randomization to receive up to 2 IM injections of study vaccine (SARS-CoV-2 rS with Matrix-M1 adjuvant or placebo) as described in [Table 3-1](#).

Cohort 1 (HIV-negative) will commence enrolment first, with vaccination starting following, and contingent on, determination of an adequate safety profile of SARS-CoV-2 rS with Matrix-M1 adjuvant through Day 35 (ie, 14 days post-second dose) in the ongoing Phase 1 portion of Protocol 2019nCoV-101 (Australia) by the global Safety Monitoring Committee (SMC) that is anticipated to be available by late July/early August 2020. Enrolment and vaccination in each cohort will be staged for the purpose of safety.

- In Cohort 1 (HIV-negative), the first 888 subjects aged ≥ 18 to < 65 years (Stage 1) will be vaccinated and followed for at least 7 days after the first dose of study vaccine (Day 7). The global SMC will review unblinded safety/reactogenicity data through Day 7 to assess prespecified vaccination pause rules to allow commencement of vaccination in the remaining subjects aged ≥ 18 to < 85 years (Stage 2) of Cohort 1 (HIV-negative) and to commence concurrent vaccination of the first 80 subjects (Stage 1) of Cohort 2 (HIV-positive). NOTE: subjects aged ≥ 65 to < 85 years will only be enrolled during Stage 2 of Cohort 1.
- In Cohort 2 (HIV-positive), the first 80 subjects (Stage 1) will be vaccinated and followed for at least 7 days after the first dose of study vaccine (Day 7). The global SMC will review unblinded safety/reactogenicity data through Day 7 to allow prespecified vaccination pause rules to allow commencement of vaccination in the remaining 160 subjects (Stage 2) in Cohort 2 (HIV-positive).

Table 3-1 Study Vaccine Groups with Maximized Immunization Plan (Based on Phase 1/2 Data)

Cohorts/ Study Vaccine Groups	Number of Randomized Subjects	Up to 2 Vaccinations		
		Day 0		Day 21
		Stage 1 ^a	Stage 2 ^a	(+ 7 days)
Cohort 1: HIV-negative subjects				
SARS-CoV-2 rS (5 µg) + Matrix-M1 adjuvant (50 µg)	N = 1480-2082 ^b	444	1036-1638	1480-1638
Placebo	N = 1480-2082 ^b	444	1036-1638	1480-1638
Cohort 2: HIV-positive subjects				
SARS-CoV-2 rS (5 µg) + Matrix-M1 adjuvant (50 µg)	N = 120	40 ^b	80	120
Placebo	N = 120	40 ^b	80	120

Abbreviations: SMC = Safety Monitoring Committee; US = United States.

- ^a Vaccination of each cohort will be divided into 2 stages for purposes of safety. Stage 1 of each cohort will first vaccinate approximately 888 subjects aged 18 to < 65 years. The SMC will review safety data through Day 7 in Stage 1 of each cohort to determine progression to Stage 2, which will vaccinate the remaining subjects aged 18 to < 85 years in Cohort 1. NOTE: subjects aged ≥ 65 to < 85 years will only be enrolled during Stage 2 of Cohort 1.
- ^b A maximum of approximately 2,082 subjects per vaccine group in Cohort 1 may be enrolled (ie, up to a total of 4,164 subjects in Cohort 1).
- ^c Stage 1 enrolment for Cohort 2 will begin concurrently with Stage 2 enrolment of Cohort 1.

The study will consist of a screening period (Days -45 to 0); vaccination days (up to 2; Days 0 and 21); outpatient study visits on Days 0, 21 (+ 7 days), and 35 (+ 7 days); at 3 and 6 months (± 15 days) after the last vaccination; and an EOS telephone call at 12 months (± 15 days) after the last vaccination. The duration of the study, excluding screening, is approximately 12 months after the last vaccination (386 days for 2 vaccinations). At the completion of the study, subjects receiving placebo will have the option of receiving SARS-CoV-2 rS with Matrix-M1 adjuvant if acceptable safety and VE have been demonstrated.

A global SMC was convened to oversee the safety of the ongoing Phase 1/2 study (Protocol 2019nCoV-101) and will oversee one or more additional studies across the SARS-CoV-2 rS vaccine program. The global SMC will be asked to provide oversight for the current study. A senior South African scientist will be asked to join the global SMC for purposes of oversight of this study. A separate SMC may be convened for this study in case the global SMC is unavailable. In either case, the designated SMC will monitor the safety of subjects in the study and will follow an SMC charter. The SMC will review unblinded safety and reactogenicity data through Day 7 of Stage 1 of each cohort to assess vaccination pause rules to allow advancement from Stage 1 vaccination to Stage 2 vaccination as previously described. The SMC will convene to perform safety reviews on a scheduled basis; for immediate concerns regarding safety observations during this study; and as needed.

Due to the ongoing pandemic, recent national regulatory and local Institutional Review Board and public health guidance will be applied at the site locations regarding alternations

in the ability of study subjects to attend an investigational site for protocol-specified visits, with the site's investigator being allowed to conduct safety assessments (eg, telephone contact, alternative location for assessment, including local laboratories or imaging centers) when necessary and feasible, as long as such visits are sufficient to assure the safety of study subjects. Serum samples may be drawn using local phlebotomy services, home health, or other modalities if 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 clinical site depending on the pandemic situation (eg, home vaccinations).

Vaccination Pause Rules:

Vaccination pause rules based on reactogenicity, AEs, and SAEs related to study participation will be in place to monitor subject safety during the study and govern advancement from Stage 1 to Stage 2 vaccination in each cohort based on assessment by the SMC.

AEs meeting any one of the following criteria will result in a hold being placed on subsequent vaccinations pending further review by the SMC and the sponsor:

- The occurrence of 2 or more related SAEs (final assessment by the sponsor per United States Food and Drug Administration (FDA) Center for Biologics Evaluation and Research Guidance) in a given MedDRA system organ class within the first 7 days (Day 7) following Stage 1 vaccination in each cohort.
- Any toxicity grade 3 (severe) solicited (local or systemic) single AE term occurring in $\geq 10\%$ of subjects in the SARS-CoV-2 rS group within the first 7 days (Day 7) following Stage 1 vaccination in each cohort.
- Any grade 3 (severe) unsolicited single AE preferred term for which the investigator assesses as related that occurs in $\geq 5\%$ of subjects in the SARS-CoV-2 rS group, within the first 7 days (Day 7) following Stage 1 vaccination in each cohort.

The sponsor, along with medical monitor, may request an SMC review for any safety concerns that may arise in the study, even if they are not associated with any specific pause rule.

3.1 SCHEDULE OF EVENTS

Table 3-2 Schedule of Events

Study Period:	Screening Period		Clinic Visits					Months After Last Vaccination		
	Study Day: -45 to 0	-5 to 0	0 ^a	7	21	35	Unscheduled	3	6	12
Window (days): ^c	-	-	0	+1	+7	+7		± 15	± 15	± 15
Minimum days following most recent vaccination: ^c	-	-	0	7	21	14		-	-	-
Study Visit:	S1	S2 ^y	1	2	3	4		5	6	EOS ^b
Informed consent	X									
Medical history ^d	X									
Inclusion/exclusion criteria	X		X ^{e,f}		X ^{e,f}					
Demographics ^g	X									
Prior/concomitant medications ^h	X		X ^{e,f}	X	X ^{e,f}	X	X	X ⁱ	X ⁱ	X ⁱ
Vital sign measurements	X		X ^j	X	X ^j					
Urine pregnancy test (WOCBA) ^k	X		X ^f		X ^f					
Serum FSH (as directed by principal investigator request only) ^l	X									
HIV testing ^m	X									
HIV viral load, CD4+, and CD8+ (Cohort 2 [HIV-positive] only) ⁿ	X							X	X	
Serology (not exclusionary for entry) ^o	X									
Physical examination ^p	X		X ^f	X	X ^f	X	X			
Vaccination			X		X					
Reactogenicity ^q			X	X	X	X ^r				
Subject diary distribution ^r			X		X					
Subject diary review and collection ^r				X		X				
Monitoring (active/passive surveillance) for COVID-19 endpoints (every 2 weeks through 01 December 2020, then every 4 weeks thereafter until EOS) ^s					From Day 8 to EOS					
FLU-PRO ^t			For 10 days, starting from the day of the new onset of symptoms of suspected COVID-19							

Study Period:	Screening Period		Clinic Visits					Months After Last Vaccination		
	Study Day:	-45 to 0	-5 to 0	0 ^a	7	21	35	Unscheduled	3	6
Window (days): ^c	-	-	0	+1	+7	+7	± 15		± 15	± 15
Minimum days following most recent vaccination: ^c	-	-	0	7	21	14	-		-	-
Study Visit:	S1	S2 ^y	1	2	3	4		5	6	EOS ^b
Nasal swab(s) - mid-turbinate and/or nasopharyngeal (qualitative PCR) ^u		X	X ^f	At all scheduled visits and during COVID-19 Surveillance Visits (Initial and Follow-Up)						
Pulse oximetry	X		X	X	X	X	X	X	X	
Blood sampling for SARS-CoV-2 immunogenicity (ELISA) – IgG, hACE2 receptor binding inhibition, and antibodies to other non-vaccine viral antigens (eg, anti-N antibodies) (or other assays developed in the future) ^v			X ^f		X ^f	X		X	X	
Blood sampling for SARS-CoV-2 neutralization assay			X ^f			X		X	X	
All unsolicited AEs			X	X	X	X				
MAAEs ^z			X	X	X	X	X	X	X	X
SAEs			X	X	X	X	X	X	X	X
AESI ^w			X	X	X	X	X	X	X	X
EOS form ^x										X

Abbreviations: AE = adverse event; AESI = adverse event(s) of special interest; anti-N antibodies = anti-nucleocapsid antibodies; BMI = body mass index; BP = blood pressure; CD = cluster of differentiation; COVID-19 = coronavirus disease 2019; ELISA = enzyme-linked immunosorbent assay; EOS = end of study; FDA = United States Food and Drug Administration; FLU-PRO = InFLUenza Patient-Reported Outcome (questionnaire); FSH = follicle-stimulating hormone; HEENT = head, eye, ear, nose, and throat (exam); HIV = human immunodeficiency virus; hACE2 = human angiotensin-converting enzyme 2; ID = identification; IgG = immunoglobulin G; MAAE = medically attended adverse event; PCR = polymerase chain reaction; PIMMC = potential immune-mediated medical conditions; S1 = Screening Visit 1; S2 = Screening Visit 2; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WOCBA = women of childbearing age.

- ^a If screening and randomization occur on the same day (ie, Day 0), study visit procedures should not be duplicated.
- ^b EOS telephone call. Should subjects decide to terminate early, an EOS telephone call will occur to collect the maximum safety data possible.
- ^c 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 subjects to continue without protocol deviation. Visit schedules following the second vaccination are calculated relative to the day the vaccinations were received.
- ^d Including prior and concomitant medical conditions, recent vaccinations (≤ 90 days), and significant surgical procedures.
- ^e Specific exclusions to vaccination will be assessed. Should subjects start specific medications or have specific diagnoses that are exclusionary at baseline, approval for vaccination must be given by medical monitor or sponsor.
- ^f Performed prior to vaccination.
- ^g Screening only. Including date of birth (day, month, and year), sex, race, ethnicity, weight, height, and BMI (derived).
- ^h Recent and current medications at the time of screening to be reviewed to ensure eligibility criteria are fulfilled. Concomitant medications include all medications (including vaccines) taken by the subject.
- ⁱ Only those medications associated with any MAAE attributed to vaccine, potential AESI, or SAE will be recorded.

Study Period:	Screening Period		Clinic Visits				Months After Last Vaccination						
	Study Day:	Window (days): ^c	Minimum days following most recent vaccination: ^c	Study Visit:	S1	S2 ^v		1	2	3	4	5	6
	-45 to 0	-5 to 0	0 ^a	7	21	35	Unscheduled	3	6	12			
	-	-	0	+1	+7	+7		± 15	± 15	± 15			
	-	-	0	7	21	14		-	-	-			
	S1	S2 ^v	1	2	3	4		5	6	EOS ^b			

- ^j On vaccination days, vital sign measurements will be collected once before vaccination to ensure subject has controlled BP and heart rate and no evidence of fever prior to vaccination. Vital sign measurements will also be collected once at 30 minutes (± 15 minutes) after vaccination to check for any reactions to the vaccine.
- ^k Women of childbearing age only. A urine pregnancy test will be performed at screening and prior to each vaccination. A serum pregnancy test may be used at screening or at the discretion of the investigator. A positive urine pregnancy test at any time will result in the subject not receiving any further vaccination.
- ^l Females only. A serum FSH test may be performed at screening to confirm postmenopausal status.
- ^m All subjects will undergo an HIV test assay approved in South Africa and performed at a central laboratory.
- ⁿ Cohort 2 (HIV-positive subjects) only. Subjects will have CD4+ and HIV-1 viral load assessments. HIV-1 viral load will be used to confirm they do not have moderate or severe immunosuppression prior to vaccination (see eligibility criteria).
- ^o Blood samples for other serology (hepatitis B and hepatitis C) will be collected at baseline but will not be used for inclusion/exclusion for randomization as a medical history will suffice; however, individuals with positive serologies (hepatitis B or hepatitis C) will not be included in the primary and secondary immunogenicity analyses.
- ^p Examination at screening to include height and weight (calculated BMI); HEENT, neck, thyroid, lungs, heart, cardiovascular, abdomen, lymph nodes of the upper extremities and neck; and musculoskeletal system/extremities to allow for vaccination; symptom-directed (targeted) physical examination at all other scheduled time points but always to include lymphatic assessment of injected upper extremity on vaccination days. Interim physical examinations will be performed at any unscheduled visit at the discretion of the investigator, if necessary.
- ^q On vaccination days, subjects will remain in clinic for 30 minutes (± 15 minutes) to be monitored for any severe reactogenicity. Severe reactions will be noted as AEs on day of vaccination.
- ^r All subjects will record reactogenicity starting on the same day of the vaccinations and for an additional 6 days in the subject diary (Days 0 to 6 and Days 21 to 27). Site personnel will review the information from the subject diary to ensure completeness. Should any reactogenicity event (toxicity grade ≥ 1) extend beyond the last day of diary collection (ie, Day 6 or Day 27), then it will be recorded as an unsolicited AE with a start date of Day 7 or Day 28 and followed to resolution per FDA guidelines for dataset capture.
- ^s Beginning on Day 8, subjects will enter active and passive surveillance for suspected COVID-19. Surveillance will include provision of a Study ID Card that provides details on study participation, study site contact information, and assessment of symptoms of suspected COVID-19 (see Table 2-2 for list of symptoms) using the FLU-PRO questionnaire. The Study ID Card should be presented to healthcare providers not affiliated with the study who encounter subjects with symptoms of suspected COVID-19. Active surveillance (applicable from Day 8 through EOS) will include outbound calls made by site staff every 2 weeks from Day 8 post first vaccination to 01 December 2020 (or longer until the local epidemic is no longer deemed to be active in the judgement of the sponsor) and every 4 weeks thereafter until EOS to solicit symptoms of suspected COVID-19 using an ethics committee approved script. Newly discovered symptoms of suspected COVID-19 will trigger a COVID-19 Surveillance Visit (Initial and Follow-Up) at the study site or at home for evaluation (as described in the COVID-19 Surveillance Visit). Passive surveillance (applicable from Day 8 through EOS) will include: a) Instructions to subjects to contact the study site within 24 hours for symptoms of suspected COVID-19; b) Weekly reminder text messages from Day 8 post first vaccination to 01 December 2020 (or longer until the local epidemic is no longer deemed to be active in the judgement of the sponsor) and every 2 weeks thereafter until EOS to remind subjects to call the study site if they develop symptoms of COVID-19; c) Newly-discovered symptoms of suspected COVID-19 will trigger a COVID-19 Surveillance Visit (Initial and Follow-Up) at the study site or at home for evaluation (as described in COVID-19 Surveillance Visit); and d) If the initial evaluation of the symptoms of suspected COVID-19 is performed by a healthcare provider not affiliated with the study (eg, in an urgent care clinic, emergency room, outpatient clinic, ad hoc COVID-19 treatment facility, etc), he/she should notify the study staff of the subject's status as per the information provided on the Study ID Card. The study staff once notified will trigger a COVID-19 Surveillance Visit (Initial and Follow-Up).
- ^t Symptoms of suspected COVID-19 will be assessed on a daily basis for 10 days using the FLU-PRO questionnaire, starting from the day of the new onset of symptoms.

Study Period:	Screening Period		Clinic Visits				Months After Last Vaccination			
Study Day:	-45 to 0	-5 to 0	0^a	7	21	35		3	6	12
Window (days):^c	-	-	0	+1	+7	+7	± 15	± 15	± 15	
Minimum days following most recent vaccination:^c	-	-	0	7	21	14	-	-	-	
Study Visit:	S1	S2^y	1	2	3	4	Unscheduled	5	6	EOS^b

^u A nasal swab will be performed at each scheduled visit, and during COVID-19 Surveillance Visits (Initial and Follow-Up) triggered by symptoms of suspected COVID-19. This includes an additional screening visit within 5 days prior to study vaccination to exclude subjects recently infected with SARS-CoV-2.

^v Subjects testing negative or positive for COVID-19 antibodies at baseline will have immune responses assessed/reported separately, unless otherwise specified.

^w AESI: To include PIMMC, COVID-19 diagnosis with sequelae, or any newly identified potential AESI followed through 365 days after final vaccination.

^x EOS form will be completed for all subjects, including those who are terminated early.

^y Subjects may complete their S1 procedures on S2.

^z MAAEs are to be collected from the time of first study vaccination until Day 35, and MAAEs assessed as related to study vaccination from the time of first study vaccination until completion of the study.

4. STUDY POPULATION

This study comprises 2 subject populations: 1) healthy HIV-negative adult male or nonpregnant female subjects (Cohort 1) and 2) medically stable HIV-positive adult male or nonpregnant female subjects (Cohort 2). A minimum of approximately 3,200 to a maximum of approximately 4,404 subjects aged ≥ 18 to < 85 years will be randomized in a blinded fashion at up to 15 sites across South Africa. Subjects in each cohort will be randomized in a 1:1 ratio via block randomization to receive SARS-CoV-2 rS with Matrix-M1 adjuvant or placebo. In Cohort 1 (HIV-negative subjects), 1,480 to 2,082 subjects each will be vaccinated in each group; in Cohort 2 (HIV-positive subjects), 120 subjects each will be vaccinated in each group.

4.1 INCLUSION CRITERIA

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

1. Adult male or female aged ≥ 18 to < 65 years at screening for Cohorts 1 and 2, and adult male or female aged ≥ 65 to < 85 years at screening for Cohort 1 only.
2. The subject has a body mass index (BMI) of 17 to 40 kg/m², inclusive, at screening.
3. Willing and able to give informed consent prior to study enrolment and comply with study procedures, including potential home visits for COVID-19 follow-up.
4. Female subjects of childbearing potential (defined as any female 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 or documented plasma follicle-stimulating hormone level ≥ 40 mIU/mL]) must agree to be heterosexually inactive from at least 21 days prior to enrolment and through 6 months after the last vaccination OR agree to consistently use any of the following methods of contraception from at least 21 days prior to enrolment and through 6 months after the last vaccination:
 - a. Condoms (male or female) with spermicide (if acceptable in country)
 - b. Diaphragm with spermicide
 - c. Cervical cap with spermicide
 - d. Intrauterine device
 - e. Oral or patch contraceptives
 - f. Norplant[®], Depo-Provera[®], or other in country regulatory-approved contraceptive method that is designed to protect against pregnancy
 - g. Abstinence, as a form of contraception, is acceptable if in line with the subject's lifestyle

NOTE: Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. These procedures and laboratory test results must be confirmed by physical examination, by subject recall of specific date and hospital/facility of procedure, or by medical documentation of said procedure.

HIV-negative subjects only (Cohort 1):

5. Documentation of HIV-negative test result by HIV test assay approved in South Africa and performed at a central laboratory.
6. Healthy at screening. Healthy status will be determined by the investigator based on medical history, vital sign measurements, and physical examination at screening.

HIV-positive subjects only (Cohort 2):

7. Receiving highly active antiretroviral therapy (HAART) and he/she has been using the same regimen within at least 8 weeks before screening. Changes in antiretroviral dosage within 8 weeks prior to entering the study are permitted. In addition, the exchange of pharmacological formulation (eg, the conventional formulation for combination formulations) is allowed.
8. Medically stable at screening, as determined by the investigator (based on review of health status, vital signs, medical history, and targeted physical examination). Vital signs must be within normal ranges prior to the first vaccination. Subjects must have been completely **free of opportunistic infections in the 1 year prior to the first study vaccination** (opportunistic infections include but are not limited to: active pulmonary or extrapulmonary tuberculosis; candidiasis of bronchi, trachea, esophagus, or lungs; invasive cervical cancer; coccidioidomycosis; cryptococcosis; chronic intestinal cryptosporidiosis; cytomegalovirus diseases; HIV-related encephalopathy; herpes simplex related-chronic ulcers (>1 month duration), bronchitis, pneumonitis, or esophagitis; histoplasmosis; chronic intestinal isosporiasis; Kaposi's sarcoma; lymphoma; Mycobacterium avium complex or Mycobacterium kansasii or other Mycobacterium; Pneumocystis carinii pneumonia; recurrent pneumonia, progressive multifocal leukoencephalopathy; Salmonella septicemia; toxoplasmosis of brain; or wasting syndrome due to HIV).
9. Have a HIV-1 viral load < 1000 copies/mL within 45 days of randomization.
10. Documentation of HIV-positive test result by HIV test assay approved in South Africa and performed at a central laboratory.

4.2 EXCLUSION CRITERIA

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

1. Any ongoing, symptomatic acute illness requiring medical or surgical care or chronic illness (excluding HIV in HIV-positive subjects) that required changes in medication in the past 2 months indicating that chronic illness/disease is not stable (at the discretion of the investigator). This includes any current workup of undiagnosed illness that could lead to a new condition.
2. Chronic disease inclusive of:
 - a. Hypertension (elevated blood pressure) \geq grade 2 (systolic blood pressure [BP] \geq 160 mmHg; and/or diastolic BP \geq 100 mmHg) according to the South African Hypertension Society's Practice Guidelines [[Seedat 2014](#); [Rayner 2019](#)];
NOTE: Hypertension [elevated BP] \leq grade 1 (systolic BP \leq 159 mmHg; diastolic BP \leq 99 mmHg) according to the South African Hypertension Society's Practice Guidelines is NOT exclusionary [[Seedat 2014](#); [Rayner 2019](#)].
 - b. Congestive heart failure with a history of an acute exacerbation of any severity in the prior 2 years;
 - c. Chronic obstructive pulmonary disease (COPD) with a history of an acute exacerbation of any severity in the prior 2 years;
 - d. In the past 3 months, evidence of unstable coronary artery disease as manifested by cardiac interventions (eg, cardiac stent placement, coronary artery bypass graft surgery [CABG]), new cardiac medications for control of symptoms, or unstable angina;
NOTE: Stable coronary heart disease is NOT exclusionary.
 - e. Asthma requiring regular/chronic control medication (eg, short-acting beta2-agonist [SABA] $>$ 2 days per week; or any chronic use of inhaled corticosteroids [ICS], long-acting beta2-agonist [LABA], leukotriene receptor antagonist [LTRA], or oral corticosteroids), and/or worsening of asthma symptoms in the past 3 months;
NOTE: Asthma not requiring regular/chronic control medication, and not requiring SABA $>$ 2 days per week, and not demonstrating worsening of symptoms in the past 3 months, will NOT be excluded.
 - f. Type 1 or type 2 diabetes (adult onset) requiring insulin;
NOTE: Non-insulin dependent type 2 diabetes is NOT exclusionary.
 - g. Chronic kidney disease/renal insufficiency;
 - h. Chronic gastrointestinal and hepatic diseases; or

- i. Chronic neurological diseases (such as multiple sclerosis, dementia, transient ischemic attacks, Parkinson's disease, degenerative neurological conditions, neuropathy, or epilepsy), history of stroke within 12 months with residual symptoms, or previous neurological disorder within 12 months with residual symptoms;
NOTE: History of migraine or chronic headaches or nerve root compression that have been stable on treatment for the last 4 weeks are NOT exclusionary.
3. Participation in research involving an investigational product (drug/biologic/device) within 45 days prior to first study vaccination.
4. Prior receipt of investigational or approved COVID-19 vaccine at any time.
5. History of a diagnosis of suspected or confirmed COVID-19.
6. Received influenza vaccination within 14 days prior to first study vaccination, or any other vaccine within 4 weeks prior to first study vaccination, or planned vaccination within 5 weeks after study first study vaccination.
7. Any autoimmune or immunodeficiency disease/condition (iatrogenic or congenital), excluding HIV in HIV-positive subjects.
NOTE: Stable endocrine disorders that have a confirmed autoimmune etiology (eg, thyroid, pancreatic), including stable diabetes not requiring insulin are allowed.
8. Chronic administration (defined as more than 14 continuous days) of immunosuppressant, systemic glucocorticosteroids, or other immune-modifying drugs within 90 days prior to first study vaccination, excluding HAART in HIV-positive subjects.
NOTE: An immunosuppressant dose of glucocorticoid is defined as a systemic dose ≥ 10 mg of prednisone per day or equivalent. The use of topical, inhaled, and nasal glucocorticoids will be permitted.
9. Received immunoglobulin, blood-derived products, or other immunosuppressant drugs within 90 days prior to first study vaccination, excluding HAART in HIV-positive subjects.
10. Acute respiratory and/or non-respiratory illness consistent with potential COVID-19 (see [Table 2-2](#) for list of symptoms) concurrent or within 14 days prior to first study vaccination (medical history and/or physical examination) or documented temperature of $> 38^{\circ}\text{C}$ during this period.
NOTE: This is a temporary exclusion for which the subject may be re-evaluated if they remain free from acute respiratory and/or non-respiratory illness consistent with potential COVID-19 after 14 days. Should a subject have a SARS-CoV-2 positive test, they may NOT be randomized.

11. Known disturbance of coagulation (iatrogenic or congenital).

NOTE: The use of low-dose aspirin (≤ 325 mg/day) as prophylaxis is acceptable in dosages consistent with local standards of care, but the use of other platelet aggregation inhibitors, thrombin inhibitors, Factor Xa inhibitors, or warfarin derivatives is exclusionary, regardless of bleeding history, because these imply treatment or prophylaxis of known cardiac or vascular disease.

12. Active cancer (malignancy) within 3 years prior to first study vaccination (with the exception of adequately treated non-melanomatous skin carcinoma, at the discretion of the investigator).

13. Any known allergies to products contained in the investigational product or latex allergy or any history of anaphylaxis in relation to any previous vaccination.

14. Women who are breastfeeding or who are pregnant at the time of screening or plan to become pregnant within the first 6 months of the study.

15. History of alcohol abuse or drug addiction within 2 years prior to the first study vaccination.

16. Any condition (other than HIV in HIV-positive subjects) that, in the opinion of the investigator, would pose a health risk to the subject if enrolled or could interfere with evaluation of the study vaccine or interpretation of study results (including neurologic or psychiatric conditions deemed likely to impair the quality of safety reporting).

17. Study team member or first-degree relative of any study team member (inclusive of sponsor, and site personnel involved in the study).

4.3 OTHER CONSIDERATIONS

Subjects meeting any of the following criteria may be delayed for subsequent vaccination:

- Respiratory symptoms in the past 3 days (ie, temperature of $> 38^{\circ}\text{C}$, cough, sore throat, difficulty breathing). Subject may be vaccinated once all symptoms have been resolved for > 3 days, although should have tested negative for COVID-19. Out of window vaccination is allowed for this reason.
- Any acute illness (eg, gastroenteritis, migraine, urinary tract infection, injury) that is causing symptoms that could, in the opinion of the investigator, impact the assessment of reactogenicity. Subject may be vaccinated once symptoms have resolved or are stabilized for > 3 days. Out of window vaccination is allowed for this reason.
- The following therapies are prohibited:
 - Routine (ie, non-emergent) vaccinations will NOT be allowed within 2 weeks of first study vaccination until 28 days after second study vaccination (Day 49).

- No chronic administration (defined as more than 14 continuous days) of any immunosuppressant medication within 3 months of first study vaccination until the last study visit (except topical, inhaled, and nasal steroids; or short-term oral steroids [course lasting \leq 14 days]). The use of topical, inhaled, and nasal glucocorticoids will be permitted if other chronic disease conditions are not exclusionary.
- No continuous use of anticoagulants, such as coumarins and related anticoagulants (ie, warfarin) or novel oral anticoagulants/anti-platelet agents. Use of \leq 325 mg of aspirin per day as prophylaxis is permitted.

NOTE: Routine medical standards of care are permitted, including vaccines needed for emergent indications (eg, tetanus booster in response to a penetrating injury).

- Subjects having any symptoms or signs of suspected COVID-19 infection ([Table 2-2](#)) that may also be due to post-vaccination reactogenicity within 7 days of **Day 0** study vaccine dose (ie, Days 0-6 following the first dose) will NOT be required to be tested for SARS-CoV-2 PCR. However, subjects having any symptoms or signs of suspected COVID-19 infection ([Table 2-2](#)) that may also be due to post-vaccination reactogenicity within 7 days of **Day 21** study vaccine dose (ie, Days 21-27 following the second dose) will be required to be tested for SARS-CoV-2 PCR according to COVID-19 standard surveillance procedures ([Section 6.1.3.3](#) and [Section 6.1.3.5](#)).
- Any subject with a new positive PCR-confirmed SARS-CoV-2 infection occurring from Day 0 and prior to second study vaccination will not be removed from the study and should receive the second study vaccination but must meet health requirements before receiving the second study vaccination (see first 2 bullets in this section).

4.4 WITHDRAWAL OF SUBJECTS FROM THE STUDY

4.4.1 Reasons for Withdrawal

Subjects can withdraw consent and discontinue from the study at any time, for any reason. Subjects 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, subject contact could be managed via telemedicine contact (eg, telephone, web chat, video, FaceTime).

The investigator may **withhold** further vaccination from a subject in the study if the subject:

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 **required**).

The investigator can also withdraw a subject 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 future vaccination.

4.4.2 Handling of Withdrawals

Subjects are free to withdraw from the study at any time upon request. Subject participation in the study may be stopped at any time at the discretion of the investigator or at the request of the sponsor.

When a subject withdraws from the study, the reason(s) for withdrawal shall be recorded by the investigator on the relevant page of the electronic case report form (eCRF). Whenever possible, any subject who withdraws from the study prematurely will undergo all EOS assessments. Any subject who fails to return for final assessments will be contacted by the site in an attempt to have them comply with the protocol. The status of subjects who fail to complete final assessments will be documented in the eCRF.

4.4.3 Replacements

Subjects 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. Subjects who receive study vaccine and subsequently withdraw, are discontinued from further vaccination, are terminated from the study, or are lost to follow-up will not be replaced.

5. STUDY TREATMENTS

5.1 VACCINES ADMINISTERED

Study vaccinations (SARS-CoV-2 rS with Matrix-M1 adjuvant or placebo) will comprise up to 2 IM injections (Day 0 and Day 21), ideally in alternating deltoids, with the study vaccine assigned in a full dose injection volume of approximately 0.5 mL. For both Cohort 1 (HIV-negative) and Cohort 2 (HIV-positive), the dose level will be 5 µg SARS-CoV-2 rS with 50 µg Matrix-M1 adjuvant (mixed in clinic or previously co-formulated). All vaccinations will be administered on an outpatient basis by designated site personnel in a way to maintain the blind. Any pharmacy preparation with unblinded product will require unblinded site personnel who will not otherwise be involved in the study procedures or observation of subjects.

5.2 INVESTIGATIONAL PRODUCTS

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

Product	Supplied Formulation
Cohort 1: HIV-Negative Subjects	
SARS-CoV-2 rS with Matrix-M1 adjuvant	Solution for preparation for injection, at a concentration of 5 µg antigen and 50 µg adjuvant.
Placebo	Sodium chloride injection (BP, sterile), 0.9%
Cohort 2: HIV-Positive Subjects	
SARS-CoV-2 rS with Matrix-M1 adjuvant	Solution for preparation for injection, at a concentration of 5 µg antigen and 50 µg adjuvant.
Placebo	Sodium chloride injection (BP, sterile), 0.9%
Abbreviations: BP = British Pharmacopoeia; SARS-CoV-2 rS = severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine.	

It is anticipated that the product will be available in a co-formulated single vial. [REDACTED]

[REDACTED] If co-formulated product is unavailable, antigen and adjuvant will be mixed in the clinic by unblinded site personnel designated to administer study vaccine.

Further details on the study vaccine can be found in the SARS-CoV-2 rS IB.

5.2.1 Investigational Product Packaging and Storage

Novavax, Inc. will provide adequate quantities and appropriate labelling of SARS-CoV-2 rS with Matrix-M1 adjuvant and PPD will ensure distribution to the clinical sites from a designated depot. Sodium chloride injection (British Pharmacopoeia, sterile) is commercially available and will be supplied by PPD. The clinical unit pharmacy will prepare the study vaccines for each subject. Detailed instructions for the preparation of study vaccine will be provided in a separate pharmacy manual.

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

5.2.2 Investigational Product Accountability

The investigator (or delegate) will maintain accurate records of receipt of all investigational product, including dates of receipt. Accurate records will be kept regarding when and how much investigational product is dispensed and used by each subject 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 investigational product accountability, all investigational product will be reconciled and retained or destroyed

according to applicable regulations. No investigational product will be destroyed until authorized in writing by the sponsor.

5.3 METHOD OF ASSIGNING SUBJECTS TO VACCINE GROUPS

Subjects will be randomly assigned in a blinded manner using the centralized Interactive Response Technology (IRT) according to pre-generated randomization schedules. Subjects in each cohort (2,400 in Cohort 1 [HIV-negative] and 240 in Cohort 2 [HIV-positive]) will be randomized in a 1:1 ratio via block randomization to receive study vaccine (SARS-CoV-2 rS with Matrix-M1 adjuvant or placebo). Details regarding the IRT process will be provided separately to the sites.

Cohort 1 (HIV-negative) will commence enrolment first, with vaccination starting following, and contingent on, determination of an adequate safety profile of SARS-CoV-2 rS with Matrix-M1 adjuvant through Day 35 (ie, 14 days post-second dose) in the ongoing Phase 1 portion of Protocol 2019nCoV-101 (Australia) by the global Safety Monitoring Committee (SMC) that is anticipated to be available by late July/early August 2020. Enrolment and vaccination in each cohort will be staged for the purpose of safety.

- In Cohort 1 (HIV-negative), the first 888 subjects aged ≥ 18 to < 65 years (Stage 1) will be vaccinated and followed for at least 7 days after the first dose of study vaccine (Day 7). The global SMC will review unblinded safety/reactogenicity data through Day 7 to assess prespecified vaccination pause rules to allow commencement of vaccination in the remaining subjects aged ≥ 18 to < 85 years (Stage 2) of Cohort 1 (HIV-negative) and to commence concurrent vaccination of the first 80 subjects (Stage 1) of Cohort 2 (HIV-positive). NOTE: subjects aged ≥ 65 to < 85 years will only be enrolled during Stage 2 of Cohort 1.
- In Cohort 2 (HIV-positive), the first 80 subjects (Stage 1) will be vaccinated and followed for at least 7 days after the first dose of study vaccine (Day 7). The global SMC will review unblinded safety/reactogenicity data through Day 7 to assess prespecified vaccination pause rules to allow commencement of vaccination in the remaining 160 subjects (Stage 2) of Cohort 2 (HIV-positive).

5.3.1 Blinding Procedures

This is an observer-blinded study. To maintain the blind, placebo vaccination via IM route will be included and unblinded site personnel will manage vaccine logistics, preparation, and administration so as to maintain the blind from the remainder of the site personnel and subjects. The unblinded site personnel will not be involved in study-related assessments or have subject contact for data collection following study vaccine administration.

5.3.2 Breaking the Blind

A subject's vaccine assignment will not be broken until the end of the study for the clinical site study team unless medical treatment of the subject depends on knowing the study vaccine the subject received. In the event that the blind needs to be broken because of a medical emergency, the investigator may unblind an individual subject's vaccine allocation.

Prior to unblinding, or as soon as possible, the investigator should contact the medical monitor to discuss the medical emergency and the reason for revealing the actual vaccine received by that subject. The vaccine assignment will be unblinded through IRT. Reasons for vaccine unblinding must be clearly explained and justified in the eCRF. The date on which the code was broken together with the identity of the person responsible must also be documented.

In addition to the aforementioned situations where the blind may be broken, the data will also be unblinded to a statistical team at specified time points for planned analyses prior to study completion, as outlined in [Section 7.5](#).

5.4 VACCINE COMPLIANCE

All doses of the study 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 clinical 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 subject has received the entire dose.

The location (right or left arm), date, and timing of all doses of study vaccine will be recorded in the subjects' eCRF. If a subject is not administered study vaccine, the reason for the missed dose will be recorded.

5.4.1 Prior Vaccinations and Concomitant Medications

Administration of medications, therapies, or vaccines will be recorded in the eCRF. Concomitant medications will include all medications (including vaccines) taken by the subject from the time of signing the ICF through EOS (or through the early termination visit if prior to that time). Prescription and OTC drugs, as well as herbals, vitamins, and supplements, will be included.

6. STUDY PROCEDURES

Before performing any study procedures, all potential subjects will sign an ICF as outlined in [Section 9.2.2.3](#). Subjects will undergo study procedures at the time points specified in the Schedule of Events (SOE; [Table 3-2](#)). The total amount of blood collected from each subject over the duration of the study, including any extra assessments that may be required, will not exceed 150 mL.

Due to the ongoing pandemic, recent national regulatory and local Institutional Review Board and public health guidance will be applied at the site locations regarding alternations in the ability of study subjects to attend an investigational site for protocol-specified visits, with the site's investigator being allowed to conduct safety and efficacy assessments (eg, telephone contact, alternative location for assessment, including local laboratories or imaging centers) when necessary and feasible, as long as such visits are sufficient to assure the safety of study subjects and site staff. Serum samples may be drawn using local phlebotomy services, home health, or other modalities if 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 clinical site depending on the pandemic situation (eg, home vaccinations).

6.1 EFFICACY ASSESSMENTS

6.1.1 Nasal Swabs for Virus Detection

Nasal swabs of the mid-turbinate and/or nasopharyngeal area for virus detection will be taken at each study visit described in the SOE ([Table 3-2](#)), and during COVID-19 Surveillance Visits (Initial and Follow-Up) triggered by symptoms of suspected COVID-19. This includes an additional screening visit within 5 days of study vaccination to exclude subjects recently infected with SARS-CoV-2.

6.1.2 Pulse Oximetry

Blood oxygen saturation levels will be measured using a portable, study provided fingertip pulse oximeter (Massimo MightySat® Rx Fingertip Pulse Oximeter, or sponsor approved equivalent in case of unavailability) at the time points specified in the SOE ([Table 3-2](#)), both for study site-based or non-study site-based pulse oximetry assessments (eg, home-based or healthcare-based Surveillance Visit).

6.1.3 Active and Passive Surveillance for Suspected COVID-19

Monitoring (active/passive surveillance) for COVID-19 endpoints will occur every 2 weeks from Day 8 through 01 December 2020 (or longer until the local epidemic is no longer deemed to be active in the judgement of the sponsor) and then every 4 weeks thereafter until EOS as described in the SOE ([Table 3-2](#)). If the national epidemic subsequently reintensifies,

then more intensive active/passive surveillance may be reinstated. The InFLUenza Patient-Reported Outcome (FLU-PRO[®]) questionnaire will be used to monitor suspected COVID-19 episodes occurring throughout the study (see [Section 6.1.3.6](#)).

Beginning on Day 8, subjects will enter active and passive surveillance for suspected COVID-19. Surveillance will include provision of a Study Identification (ID) Card that provides details on study participation, study site contact information, and assessment of symptoms of suspected COVID-19 using the FLU-PRO questionnaire. The Study ID Card should be presented to healthcare providers not affiliated with the study who encounter subjects with symptoms of suspected COVID-19.

6.1.3.1 Active Surveillance

Active surveillance, which is applicable from Day 8 through EOS, will consist of phone calls as follows:

- Outbound calls will be made by site staff every 2 weeks from Day 8 post first vaccination to 01 December 2020 (or longer until the local epidemic is no longer deemed to be active in the judgement of the sponsor) and every 4 weeks thereafter until EOS to solicit symptoms of suspected COVID-19 using an approved script. Newly discovered symptoms of suspected COVID-19 will trigger a COVID-19 Surveillance Visit (Initial and Follow-Up) at the study site or at home for evaluation (as described in the COVID-19 Surveillance Visit). If a subject has recently had a COVID-19 Surveillance Visit, then the outbound call will serve as a follow-up to document whether symptoms of suspected COVID-19 have resolved or remain ongoing.

6.1.3.2 Passive Surveillance

Passive surveillance, which is applicable from Day 8 through EOS, includes the following:

- Instructions to subjects to contact the study site within 24 hours for symptoms of suspected COVID-19.
- Weekly reminder text messages from Day 8 post first vaccination to 01 December 2020 (or longer until the local epidemic is no longer deemed to be active in the judgement of the sponsor) and every 2 weeks thereafter until EOS to remind subjects to call the study site if they develop symptoms of COVID-19 (see [Table 2-2](#) for list of symptoms).
- Newly-discovered symptoms of suspected COVID-19 (see [Table 2-2](#) for list of symptoms) will trigger a COVID-19 Surveillance Visit (Initial and Follow-Up) at the study site or at home for evaluation (as described in COVID-19 Surveillance Visit).
- If the initial evaluation of the symptoms of suspected COVID-19 is performed by a healthcare provider not affiliated with the study (eg, in an urgent care clinic,

emergency room, outpatient clinic, ad hoc COVID-19 treatment facility, etc), he/she should notify the study staff of the subject's status as per the information provided on the Study ID Card. The study staff once notified will trigger a COVID-19 Surveillance Visit (Initial and Follow-Up).

6.1.3.3 Assessment of Symptoms of Suspected COVID-19

Respiratory and non-respiratory symptoms consistent with suspected COVID-19 will be defined for all modes of surveillance by a self-reported new onset of:

- Active surveillance
 - Fever (defined by subjective or objective measure, regardless of use of anti-pyretic medications) **OR**
 - ≥ 2 COVID-19 respiratory/non-respiratory symptoms consistent with suspected COVID-19 (see [Table 2-2](#) for list of symptoms).
- Passive surveillance
 - Self-presentation for **any** respiratory/non-respiratory symptom consistent with suspected COVID-19 (see [Table 2-2](#) for list of symptoms).

EVERY episode of a “new onset” of symptoms of suspected COVID-19 will trigger a COVID-19 Surveillance Visit (Initial and Follow-Up) and will be assessed using the FLU-PRO questionnaire as described in the COVID-19 Surveillance Visit (Initial and Follow-Up).

“New onset” will require at least a preceding 7-day period free of symptoms, or with baseline symptoms, to differentiate an episode from any prior illness.

6.1.3.4 Severity of COVID-19 Symptoms

COVID-19 symptoms will be categorized as virologically confirmed, mild, moderate, or severe as described in [Table 2-1](#).

6.1.3.5 COVID-19 Surveillance Visit (Initial and Follow-up)

Procedures to occur during site or home COVID-19 Surveillance Visit (both Initial and Follow-Up) will be triggered by symptoms of suspected COVID-19 captured by active or passive surveillance.

When a subject is determined to have a new onset of **fever OR ≥ 2 COVID-19 respiratory/non-respiratory symptoms consistent with suspected COVID-19** on active surveillance **OR any COVID-19 respiratory/non-respiratory symptoms consistent with suspected COVID-19** on passive surveillance, the subject will immediately begin to assess the symptoms of suspected COVID-19 on a daily basis for 10 days using the FLU-PRO questionnaire, starting from the day of the new onset of symptoms and will be invited to

return to the study clinic as soon as possible for an Initial COVID-19 Surveillance Visit (or will be seen by an outbound home visit by study staff depending on local conditions).

6.1.3.5.1 Initial COVID-19 Surveillance Visit

An Initial COVID-19 Surveillance Visit will be performed at the study site (or home) and will occur as soon as possible within approximately **1-3 days** of new symptom onset (however, data from specimens obtained up to 14 days will be accepted). The visit will consist of the following:

- Review and confirmation of the history of suspected COVID-19 symptoms, including approximate date of onset of illness and solicitation of each symptom (see [Table 2-2](#)).
- Vital signs, including resting respiratory rate (on room air or the subject's basal level of chronic supplemental oxygen use) and pulse oximetry (using MightySat® Rx Fingertip Pulse Oximeter), will be captured as numerical values. Lung auscultation (exam) will be performed by a study physician or nurse.
- Ascertainment of any unscheduled healthcare visit by the subject (or home visit by a healthcare provider) in response to symptoms of suspected COVID-19.
- Ascertainment of new concomitant medications (especially antibiotics) or altered doses/frequencies of existing concomitant medications resulting from symptoms of suspected COVID-19.
- Collection of a specimen of upper respiratory secretions via nasal mid-turbinate swab for qualitative PCR detection of SARS-CoV-2.

If a subject is unable to come to the study site for an Initial COVID-19 Surveillance Visit due to a hospitalization, the study site staff (study physician or nurse) will make every effort to visit the subject in the hospital to perform the Initial COVID-19 Surveillance Visit assessments (ie, review of symptom history, collection of nasal swab for PCR, measurement of vital signs including pulse oximetry, lung exam, and concomitant medications).

6.1.3.5.2 Follow-Up COVID-19 Surveillance Visit

A Follow-Up COVID-19 Surveillance Visit will occur approximately 4 (+2) days after the Initial COVID-19 Surveillance Visit to monitor for progression of disease. Every Initial COVID-19 Surveillance Visit must have a corresponding Follow-up Surveillance visit. This Follow-up COVID-19 Surveillance visit will consist of the following:

- If the nasal sample from the Initial COVID-19 Surveillance Visit tests **positive** for SARS-CoV-2 virus by qualitative PCR, the subject will NOT return to the study site for re-evaluation. Instead, the study staff will conduct the **Follow-Up COVID-19 Surveillance Visit at HOME** approximately 4 (+2) days after the Initial COVID-19 Surveillance Visit to ascertain worsening/progression of COVID-19 symptoms. This follow-up home visit by study staff (performed by a study physician or nurse) will

- include all of the same procedures outlined in this section, including review of symptom history, measurement of vital signs (including pulse oximetry), and lung auscultation; however, a repeat nasal mid-turbinate swab will not be obtained since the subject has already tested positive.
- If the nasal sample from the Initial COVID-19 Surveillance Visit tests **negative** for SARS-CoV-2 by qualitative PCR or the sample is inadequate for analysis, the subject will be **re-evaluated** in the clinic (or home) approximately 4 (+ 2) days after the Initial COVID-19 Surveillance Visit to ascertain worsening/progression of suspected COVID-19 symptoms AND to obtain a **second** nasal mid-turbinate swab for qualitative PCR detection of SARS-CoV-2. This re-evaluation will include all of the same procedures outlined in this section, including review of symptom history, measurement of vital signs (including pulse oximetry), and lung auscultation.

If a subject is unable to come to the study site for an Follow-up COVID-19 Surveillance Visit due to a hospitalization, the study site staff (study physician or nurse) will make every effort to visit the subject in the hospital to perform the Follow-up COVID-19 Surveillance Visit assessments (ie, review of symptom history, collection of nasal swab for PCR, measurement of vital signs including pulse oximetry, lung exam, and concomitant medications).

After the Follow-Up COVID-19 Surveillance Visit, subjects will continue to receive telephone contacts approximately **every week** for ascertainment of COVID-19 symptom status until resolution of symptoms. Subsequent calls will document resolution or return to baseline of COVID-19 symptoms in order to calculate illness duration (date of symptom onset to day of symptom resolution) and will collect any additional healthcare visits, hospitalizations, and/or concomitant medications due to the suspected COVID-19. Once symptoms resolve, telephone contacts for active surveillance will return to every 2 or 4 weeks depending on the required frequency of active surveillance at that point in the study.

EVERY episode of a “new onset” of symptoms of suspected COVID-19 will trigger a COVID-19 Surveillance Visit (Initial and Follow-Up) and subject completion of a FLU-PRO questionnaire for 10 days.

Should a subject visit an emergency room, be admitted to the hospital or a COVID-19 ward, and active/passive surveillance symptom-triggered nasal swab collection is missed, then the local public health COVID-19 diagnostic test (or COVID-19 diagnostic test performed in the healthcare setting) will be taken as a valid result.

Importantly, following any emergency visit or hospitalization episode for suspected COVID-19, clinical data on symptoms, vital signs, exam findings, COVID-19 and other diagnostic testing, diagnoses, and complications occurring during the suspected COVID-19 emergency room and/or hospitalization episode will be collected from available medical records on a study specific hospitalization/emergency room data collection form.

If the subject's Day 0 swab tests positive by SARS-CoV-2 PCR, then the subject should (regardless of the initial presence or absence of COVID-19 symptoms): a) begin to complete the FLU-PRO questionnaire and b) receive a single HOME visit on Day 7 to complete BOTH the Follow-Up Surveillance Visit and the Day 7 Visit procedures. If a subject tests positive by SARS-CoV-2 PCR on a swab collected at a scheduled study visit (eg, Day 7, 21, 35; and at 3 and 6 months after the last vaccination), then the subject should (regardless of the initial presence or absence of COVID-19 symptoms): a) begin to complete the FLU-PRO questionnaire and b) receive a Follow-Up Surveillance Visit at HOME approximately 4 (+ 2) days later.

All surveillance nasal swab samples obtained via site staff collection will be sent to one or more designated central laboratories (eg, Clinical Laboratory Services [CLS]) using harmonized methods where a validated qualitative PCR test will be performed in near real time for detection of SARS-CoV-2.

Should a medical visit be warranted based on symptomatology and need for treatment (and allowed via local isolation guidance), such a visit may occur using telemedicine, home visitation, or clinic visit.

Subjects will be notified of positive SARS-CoV-2 results as soon as locally practicable due to requirements of self-isolation and potential transmission.

Key clinical endpoint definitions to be used are summarized below:

- **Primary infection** will be defined as the first (+) PCR regardless of symptoms in a previously seronegative subject.
- **Primary symptomatic infection** will be defined as the first (+) PCR with symptoms of COVID-19 during the previous 7 days.

Note that (+) PCR COVID-19 symptoms and events captured as efficacy endpoints will NOT be doubly recorded in the AE eCRF, unless a particular illness fulfils the definition of an SAE.

6.1.3.6 FLU-PRO

The FLU-PRO questionnaire was designed to standardize and comprehensively assess symptoms associated with various viruses across multiple body systems over the course of the disease 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.

The FLU-PRO can be completed by patients using paper/pen, electronically, or via telephone interview. It has been tested and used in studies of influenza, influenza-like illness,

respiratory syncytial virus (RSV), rhinovirus, enterovirus, and more recently COVID-19. To date, the FLU-PRO has been completed by over 4,000 patients between 12-81 years of age with adherence rates over 90%.

The 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, disturbances in smell and taste) added that have been associated with COVID-19. In the current study, subjects will complete the FLU-PRO daily for 10 days at home starting from the day of the new onset of symptoms. A 10-day FLU-PRO questionnaire should be completed for every episode of new onset of suspected COVID-19 symptoms. Each question is brief (sign or symptom only with severity rating). The entire questionnaire takes under 4 minutes each day to complete. FLU-PRO scoring includes total and subscale scores for symptom severity by body system. The instrument also provides data on the presence/absence of symptoms, symptom profiles, and change over time.

6.2 IMMUNOGENICITY ASSESSMENTS

Blood samples for immunogenicity assessments will be collected before vaccination and at selected time points following vaccination as listed in the SOE ([Table 3-2](#)).

Immune measurements (ELISA) will be conducted on serum (IgG) for SARS-CoV-2 rS protein antigen(s). Additional immunogenicity assessments specific to SARS-CoV-2 (or related variants) will include an ACE2 receptor binding inhibition assay and a neutralizing antibody assay. Serological assays may be performed to measure immune responses to 1 or more non-spike protein SARS-CoV-2 viral antigens in order to distinguish between serological responses to vaccine versus natural infection.

The details on the handling, processing, and shipping of immunogenicity samples will be provided separately in a laboratory manual.

Subjects will be asked to provide consent for the use of samples for future testing or assay development specific to SARS-CoV-2 (or related variants). Aliquots of all collected samples from this study may be retained for additional testing with antigens specific to SARS-CoV-2 (or related variants) for a maximum of 25 years (starting from the date at which the last subject had the last study visit), unless local rules, regulations, or guidelines require different timeframes or different procedures, in accord with subject consent.

6.3 SAFETY ASSESSMENTS

The timing and frequency of all safety assessments are listed in the SOE ([Table 3-2](#)).

Safety assessments will include monitoring and recording of solicited (local and systemic reactogenicity events) and unsolicited AEs; MAAEs; AESI; SAEs; vital sign measurements

on day of vaccination; physical examination findings; and occurrence of SARS-CoV-2 infection as measured by nasal mid-turbinate swab and using qualitative PCR following subject-reported symptoms. COVID-19 severity will be categorized as virologically confirmed, mild, moderate, or severe according to protocol-specified criteria (see [Table 2-1](#)). Recording of solicited and unsolicited AEs may be conducted by electronic data capture (EDC)/reporting. Monitoring for potential immune-mediated medical conditions (PIMMC) and AESI specific to potential disease enhancement for COVID-19 will also be monitored (see [Section 9.4](#) [Appendix 4] for details).

6.3.1 Adverse Events

AEs will be assessed during the study as described in the SOE ([Table 3-2](#)) and should be followed until they are resolved, stable, or judged by the investigator to be not clinically significant. AEs will be captured after the first dose of study vaccine administered with the exception of an AE related to study procedure or one that causes a delay in study vaccine administration (eg, acute illness).

The investigator is responsible for ensuring that all AEs and SAEs are recorded in the eCRF and reported to the sponsor, regardless of their relationship to study vaccine or clinical significance. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

6.3.1.1 Adverse Event Definitions

The investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study vaccination or their clinical significance.

An AE is defined as any untoward medical occurrence in a subject enrolled into this study regardless of its causal relationship to study vaccination. Subjects will be instructed to contact the investigator at any time after randomization if any symptoms develop.

6.3.1.1.1 Serious Adverse Events

An SAE is defined as any event that

- results in death
- is immediately life threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment,

they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

6.3.1.1.2 Local and General Systemic Reactogenicity Symptoms

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 ([Section 9.3](#), Appendix 3). Should any reactogenicity event extend beyond 7 days after vaccination (ie, beyond Days 0-6 or beyond Days 21-27) and be clinically significant by toxicity grade 1 or greater, then it will be recorded as an unsolicited AE with a start date on the 8th day following vaccination (ie, Day 7 or Day 28) and followed to resolution.

6.3.1.1.3 Adverse Events of Special Interest

Subjects will be assessed for diagnosis of an AESI at all study visits. AESIs include PIMMCs, AEs specific to COVID-19, or other potential AEs that may be determined at any time by regulatory authorities as additional information concerning COVID-19 is obtained. 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 [Section 9.4](#), Appendix 4.

6.3.1.1.4 Medically Attended Adverse Events

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

6.3.1.1.5 Pregnancy

Pregnancy is not considered an AE unless there is a suspicion that an investigational vaccine may have interfered with the effectiveness of a contraceptive medication. Any pregnancy that occurs during study participation must be reported using a clinical study pregnancy form. To ensure subject safety, each pregnancy must be reported to Novavax, Inc. or designee within 2 weeks of learning of its occurrence. If pregnancy occurs, further vaccination will be discontinued. The pregnancy must be followed up to determine outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and the status of both mother and child, even if the subject was discontinued from the study. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous miscarriages must be reported as an SAE.

Any pregnancy brought to the investigator's attention after the subject has completed the study but occurring while the subject was in the study must be promptly reported to:

PPD Pharmacovigilance:
24-Hour Safety Hotline Fax:

24-Hour Safety Hotline:

6.3.1.2 Eliciting and Documenting Adverse Events

At every study visit, subjects will be asked a standard question to elicit any medically-related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and OTC medications).

In addition to subject observations, AEs will be documented from any data collected on the AE page of the eCRF or other documents that are relevant to subject safety.

6.3.1.3 Reporting Adverse Events

All AEs reported or observed during the study will be recorded on the AE page of the eCRF. Information to be collected includes study vaccine, type of event, time of onset, dosage, investigator-specified assessment of severity and relationship to study vaccine and/or study procedure, time of resolution of the event, seriousness, any required treatment or evaluations, and outcome. Any AEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease must also be reported. All AEs will be followed until they are resolved, stable, or judged by the investigator to be not clinically significant. MedDRA will be used to code all AEs.

Any medical condition that is present at the time that the subject is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

Any AE that is considered serious by the investigator or that meets SAE criteria ([Section 6.3.1.1.1](#)) must be reported to the sponsor or designee immediately (within 24 hours after the investigator has confirmed the occurrence of the SAE). The investigator will assess whether there is a reasonable possibility that the study vaccine caused the SAE. The sponsor will be responsible for notifying the relevant regulatory authorities of any SAE, in compliance with health authority requirements, as outlined in the relevant clinical study guidelines. The investigator is responsible for notifying the independent Health Research Ethics Committee (HREC) directly.

For this study, the following contact information will be used for SAE reporting:

PPD Pharmacovigilance:
24-Hour Safety Hotline Fax:

24-Hour Safety Hotline:

6.3.1.4 Assessment of Severity

The severity (or intensity) of an AE refers to the extent to which it affects the subject'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 subject'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 subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

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

6.3.1.5 Assessment of Causality

The investigator's assessment of an AE's relationship to study vaccine is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

The investigator will assess causality (ie, whether there is a reasonable possibility that the study vaccine caused the event) for all AEs and SAEs (solicited reactions are to be considered as being related to vaccination). The relationship will be classified as follows:

- Not related: There is not a reasonable possibility of relationship to study vaccine. The AE does not follow a reasonable temporal sequence from administration of study vaccine or can be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications).
- Related: There is a reasonable possibility of relationship to study vaccine. The AE follows a reasonable temporal sequence from administration of study vaccine and cannot be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, or concomitant medications), represents a known reaction to study vaccine or other vaccines in its class, is consistent with the known pharmacological properties of the study vaccine, and/or resolves with discontinuation of the study vaccine (and/or recurs with re-challenge, if applicable).

6.3.1.6 Follow-up of Adverse Events

All AEs must be reported in detail on the appropriate page of the eCRF and followed until they are resolved, stable, or judged by the investigator to be not clinically significant.

6.3.2 Clinical Laboratory Testing

Clinical laboratory tests will be performed at a designated laboratory. The majority of these tests will be used for inclusion/exclusion for randomization (HIV serology and pregnancy testing).

HIV serology	Cohort 1 (HIV-negative): <ul style="list-style-type: none"> HIV test assay approved in South Africa at screening Cohort 2 (HIV-positive): <ul style="list-style-type: none"> HIV test assay approved in South Africa at screening CD4+ and HIV-1 viral load assessments
Other serology	All subjects: <ul style="list-style-type: none"> Hepatitis B surface antigen, hepatitis C virus antibody
Pregnancy testing/ Postmenopausal testing	Female subjects: <ul style="list-style-type: none"> Urine pregnancy test at screening and prior to each vaccination (human chorionic gonadotropin) FSH as directed by investigator request only

Abbreviations: CD = cluster of differentiation; ELISA = enzyme-linked immunosorbent assay; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus.

Note: A serum pregnancy test may be substituted for a urine pregnancy test at screening or at the discretion of the investigator.

6.3.3 Vital Sign Measurements

Vital sign measurements will include oral temperature (or via forehead/ear reader), pulse rate, diastolic and systolic BP (after subject is seated for at least 5 minutes), respiratory rate, and pulse oximetry (using the study provided Massimo MightySat® Rx Fingertip Pulse Oximeter). Temperature will be recorded and graded during general systemic reactogenicity evaluation (Section 6.3.1.1.2). The other 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 subject has controlled blood pressure and heart rate and no evidence of fever prior to vaccination and once at 30 minutes (\pm 15 minutes) after vaccination to check for any reactions to the vaccine. The investigator will only apply standard toxicology grading on the day of vaccination, both before and after vaccination (Section 9.3, Appendix 3). If individual vital sign measurements are considered clinically significant by the investigator, vaccination may be withheld that day, and subjects may return on a subsequent day for re-evaluation and vaccination, ideally, within the time window specified in the SOE (Table 3-2).

6.3.4 Physical Examinations

A physical examination will be performed at screening (at minimum, assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular, abdomen, lymph nodes of the upper extremities and neck, and musculoskeletal system/extremities). Height and weight will be measured and BMI will be calculated at screening only.

A targeted or symptom-directed physical examination will be performed at the time points specified in the SOE ([Table 3-2](#)).

6.3.5 Safety Monitoring

Safety oversight will be conducted by an SMC during the course of the study. The SMC that is an independent group of experts that monitors subject safety and advises Novavax, Inc. The SMC members will be separate and independent of site personnel participating in this study and should not have a scientific, financial, or other conflict of interest related to this study or the sponsor. The SMC will consist of members with appropriate expertise to contribute to the interpretation of the data from this study.

The global SMC convened for the ongoing Phase 1/2 study (Protocol 2019nCoV-101) will be asked to provide oversight for the current study and will likely oversee studies across the SARS-CoV-2 rS vaccine program. A senior South African scientist will be asked to join the global SMC for purposes of oversight of this study. A separate SMC may be convened for this study in case the global SMC is unavailable. In either case, the designated SMC will monitor the safety of subjects in the study and will follow an SMC charter. The SMC will review unblinded safety and reactogenicity data through Day 7 of Stage 1 of each cohort to assess vaccination pause rules to allow advancement from Stage 1 vaccination to Stage 2 vaccination as previously described. The SMC will convene to perform safety reviews on a scheduled basis; for immediate concerns regarding safety observations during this study; and as needed.

The global SMC will operate under the rules of a sponsor-approved charter that will be approved at the organizational meeting of the SMC. At this time, each data element that the SMC needs to assess will be clearly defined. Procedures for SMC reviews/meetings will be defined in the charter. The SMC will review applicable data for safety assessments (AEs by classifications) and any clinical data that may be of significance to this review (eg, demographics, vaccination timing, and medications). Additional data may be requested by the SMC, and interim statistical reports may be generated as deemed necessary and appropriate for this review. The SMC may receive data in aggregate and presented by vaccine group. The SMC may also be provided with expected and observed rates of the expected AEs in an unblinded fashion and may request the vaccine assignment be unblinded for an individual subject if required for safety assessment. The SMC Charter will establish enhanced disease monitoring guidelines associated with ongoing guidance documents.

7. STATISTICAL ANALYSIS PLANS

7.1 SAMPLE SIZE CALCULATIONS

This study is designed to enroll a minimum of approximately 3,200 to a maximum of approximately 4,404 subjects divided among 2 cohorts as follows:

- Approximately 2,960 to 4,164 subjects ≥ 18 to < 85 years in Cohort 1 (HIV-negative) that include a minimum of approximately 1,480 to 2,082 subjects receiving SARS-CoV-2 rS with Matrix-M1 adjuvant.
- Approximately 240 subjects ≥ 18 to < 65 years in Cohort 2 (HIV-positive) that include a minimum of approximately 120 subjects receiving SARS-CoV-2 rS with Matrix-M1 adjuvant.

The target sample size of 1,480 to 2,082 actively-immunized subjects in Cohort 1 (HIV-negative) is sufficient to detect an AE rate of at least 1 in 625 subjects (ie, background rates of 0.16%) with 90% probability.

The target sample size of 120 actively-immunized subjects in Cohort 2 (HIV-positive) is sufficient to detect an AE rate of at least 1 in 53 subjects (ie, background rates of 1.9%) with 90% probability.

Power calculations were performed using the two-sided 97.5% CIs (ie, one-side alpha of 0.0125) to be conservative. Cohort 1 (HIV-negative) is designed to provide at least 80% power for each of the 2 independent primary endpoints based on the following assumptions (Table 7-1):

1. A symptomatic COVID-19 incident rate of 5% in the placebo group and a VE of 60%.
2. A symptomatic moderate or severe COVID-19 incident rate of 2.5% in the placebo group and a VE of 80%.
3. 90% evaluability rate for the per-protocol efficacy (PP-EFF) population (assuming 10% unevaluable due to attrition and/or baseline-seropositive subjects).

Table 7-1 Sample Size Needed for 80% Power

Independent Primary Endpoints ^a	Placebo Attack Rate	Vaccine Efficacy	LBCI Success Criteria	Enrolled Sample Size ^b		
				Per Group Size	Total Size	Number of Events
Any COVID-19 Symptoms	5%	30%	> 0%	3819	7638	292
	5%	40%		2027	4054	146
	5%	50%		1219	2438	82
	5%	60%		792	1584	50
	5%	70%		541	1082	32
	5%	80%		383	766	21
	4.5%	30%		4262	8524	293
	4.5%	40%		2261	4522	147
	4.5%	50%		1360	2720	83
	4.5%	60%		883	1766	50
	4.5%	70%		603	1206	32
	4.5%	80%		428	856	21
	4.0%	30%		4817	9634	295
	4.0%	40%		2554	5108	147
	4.0%	50%		1536	3072	83
	4.0%	60%		997	1994	50
	4.0%	70%		681	1362	32
4.0%	80%	482	964	21		
Moderate or Severe COVID-19 Symptoms	2.5%	50%	> 0%	2487	4974	84
	2.5%	60%		1613	3226	51
	2.5%	70%		1102	2204	32
	2.5%	80%		779	1558	21
	2.0%	50%		3120	6240	84
	2.0%	60%		2024	4048	51
	2.0%	70%		1382	2764	32
	2.0%	80%		978	1956	21

Abbreviation: CI = confidence interval; LBCI = lower bound of the confidence interval; PP-EFF = per-protocol efficacy.

^a Each endpoint to be tested at one-sided alpha of 0.0125 (ie, lower bound of two-sided 97.5% CI).

^b Accounting for 90% evaluability rate for the PP-EFF population.

Based on the above assumptions, the minimum target numbers of endpoints needed are 50 symptomatic mild, moderate, or severe COVID-19 endpoints or 21 symptomatic moderate or severe COVID-19 endpoints. [Table 7-2](#) summarizes the power calculations for the two primary endpoints based on the proposed multiplicity adjustment using Hochberg method and the single primary endpoint without an adjustment based on the target numbers of

endpoints determined. The following power calculations were performed by 10,000 simulated trials that were created under various assumptions of vaccine efficacies.

Table 7-2 Power For 50 Mild, Moderate, or Severe COVID-19 Endpoints and 21 Moderate or Severe COVID-19 Endpoints

Assume Vaccine Efficacy		Power for 2 Primary Endpoints using Hochberg Method			Power for Single Primary Endpoint Without Multiplicity Adjustment	
Mild, Moderate, or Severe COVID-19 Symptoms	Moderate or Severe COVID-19 Symptoms	Mild, Moderate, or Severe COVID-19 Symptoms	Moderate or Severe COVID-19 Symptoms	At least 1 Endpoint	Mild, Moderate, or Severe COVID-19 Symptoms	Moderate or Severe COVID-19 Symptoms
60%	80%	87.24%	87.62%	93.43%	90.31%	87.62%
50%	60%	54.88%	41.13%	59.96%	69.76%	41.13%
50%	70%	61.39%	65.07%	74.18%	70.19%	65.07%
60%	70%	81.67%	64.05%	84.36%	90.08%	64.05%

Abbreviations: COVID-19 = coronavirus disease 2019.

The actual sample size for the study will be selected based on operational considerations given the evolving pandemic conditions in South Africa.

7.2 ANALYSIS SETS

The intent-to-treat efficacy (ITT-EFF) and immunogenicity (ITT-IMM) analysis sets will include all subjects who are randomized and receive at least 1 dose study vaccine (SARS-CoV-2 rS with Matrix-M1 adjuvant or placebo), regardless of protocol violations or missing data. The intent-to-treat (ITT) analysis set will be used as a supportive analysis population for the immunogenicity and efficacy analyses and will be analyzed according to the study vaccine group as randomized.

The safety analysis set will include all subjects who receive at least 1 dose of study vaccine (SARS-CoV-2 rS with Matrix-M1 adjuvant or placebo). Subjects in the safety analysis set will be analyzed according to the vaccine actually received.

The PP-EFF will include seronegative subjects who receive both doses of study vaccine (SARS-CoV-2 rS with Matrix-M1 adjuvant or placebo) and have no major protocol deviations affecting the primary efficacy outcome as assessed by the sponsor prior to unblinding. All analyses of the PP-EFF population will exclude any illness episodes with positive SARS-CoV-2 by any validated PCR or antibody test occurring before from 7 days after the second vaccine dose (eg, Day 28).

The per-protocol immunogenicity (PP-IMM) analysis set will include subjects who receive both doses of study vaccine (SARS-CoV-2 rS with Matrix-M1 adjuvant or placebo), have at least a baseline and 1 serum sample result available after vaccination, are negative for hepatitis B and C, and have no major protocol violations that are considered clinically relevant to impact immunogenicity response at the corresponding study visit as assessed by

the sponsor prior to unblinding. For each visit, the SARS-CoV-2 unexposed population will also exclude any illness episodes with positive SARS-CoV-2 by any validated PCR or antibody test prior to each visit. Prior-exposed subjects will be determined using baseline SARS-CoV-2 immunity defined as positive SARS-CoV-2 by qualitative PCR or serum IgG antibody at baseline, or positive SARS-CoV-2 by qualitative PCR through Day 21 or Day 35, according to the specified analysis. Analysis will be performed to assess if immune responses differ between exposed and unexposed individuals (ie, whether prior exposure alters dosing regimen considerations in a pandemic response).

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

7.3 STATISTICAL ANALYSIS

Details of all statistical analyses will be described in a statistical analysis plan (SAP).

All data collected will be presented in data listings. Data from subjects excluded from an analysis set will be presented in the data listings but not included in the calculation of summary statistics for that analysis set.

For categorical variables, frequencies and percentages will be presented. Continuous variables will be summarized using descriptive statistics (number of subjects, mean, median, minimum, and maximum).

Baseline demographic and background variables will be summarized by study vaccine group. The number of subjects who enroll in the study and the number and percentage of subjects who complete the study will be presented. Frequency and percentage of subjects who withdraw or discontinue from the study, and the reason for withdrawal or discontinuation, will also be summarized.

7.3.1 Efficacy Analyses

The 2 independent primary efficacy endpoints will be analyzed on the ITT-EFF and PP-EFF populations. Conclusions concerning declaration of attainment of the primary efficacy endpoint at the completion of the study will only be based on the PP-EFF population. In addition, supportive analyses based on the ITT-EFF population will also be performed.

The VE is defined as $VE (\%) = (1 - RR) \times 100$, where RR = relative risk of incidence rates between the 2 study vaccine groups (SARS-CoV-2 rS with Matrix-M1 adjuvant or placebo). The official (ie, event-driven) analysis for the primary objective in the PP-EFF population will be carried out at an overall one-sided Type I error rate of 0.025 for the 2 independent primary endpoints. Since the demonstration of the primary objective can be achieved if at

least 1 of the 2 primary endpoints meets the prespecified success criteria, the statistical analysis will be performed in the following order:

1. Construct two-sided 95% CIs for the 2 primary efficacy endpoints. If both lower bounds are $> 0\%$, declare that both endpoints have met the success criteria. Otherwise, proceed to the next step.
2. Construct two-sided 97.5% CIs for the 2 primary efficacy endpoints. If the higher of the lower bounds is $> 0\%$, declare that only the endpoint associated with lower bound $> 0\%$ has met the success criterion. Otherwise, both endpoints did not meet the success criteria.

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 study 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 subject identifier. Poisson distribution will be used with a link function logarithm.

Hypothesis testing of either of the independent primary efficacy endpoints will be carried out against $H_0: VE \leq 0\%$. Rejection of the null hypothesis, $H_0: VE \leq 0\%$ demonstrates a statistically significant vaccine effect for either primary endpoint. The study will continue for the intended duration to measure immunogenicity and safety endpoints, regardless of a primary endpoint efficacy success. The official analysis of the primary efficacy endpoints will be triggered when at least 50 PP-EFF subjects with symptomatic mild, moderate, or severe COVID-19 or at least 21 PP-EFF subjects with symptomatic moderate or severe COVID-19 have accrued. Also, in order to be able to respond to the unexpected and rapidly evolving COVID-19 pandemic situation globally, other factors such as requests by government or public health agencies may also be factored into the decision-making to unblind the study for the official analysis, but this always occurs in consultation with lead regulatory agencies.

In order to address the uncertainty around the COVID-19 circulation in the study population, an active monitoring of the blinded endpoint accruals for the 2 independent primary efficacy endpoints will be performed by the sponsor. The sponsor may choose to switch 1 of the 2 primary efficacy endpoints to a secondary or exploratory efficacy endpoint prior to unblinding if it is determined that the accrual for the endpoint is likely to fall well short of the target number. The decision will be based solely on the total numbers of blinded endpoints accrued without consideration of vaccine group assignment. The decision will not be based on VE data. If this option is triggered, the remaining primary efficacy endpoint will be analyzed using one-sided Type I error rate of 0.025 (ie, two-sided 95% CI). The details for the criteria to be used to act on this option will be included in the SAP.

In addition to the official event-driven efficacy analysis, additional time-based efficacy analyses may be performed, including but not limited to through 6 and 12 months of follow-up (following last vaccination).

7.3.2 Immunogenicity Analyses

The primary and secondary immunogenicity analyses will be performed using the PP-IMM and ITT-IMM analysis populations.

For the serum antibody levels measured by anti-spike IgG ELISA, ACE2 receptor binding inhibition assay, and microneutralization assays, the geometric mean at each study visit, the GMFR comparing to the baseline (Day 0) at each post-vaccination study visit, along with 95% CI will be summarized by study vaccine group. The 95% CI will be calculated based on the t-distribution of the log-transformed values for geometric means or GMFRs, then back transformed to the original scale for presentation. The SCR (proportion of subjects with ≥ 4 -fold rises if naïve at baseline and ≥ 2 -fold rise in ELISA units if SARS-CoV-2 exposed at baseline), and SRR (proportion of subjects with rises in ELISA units exceeding the 95th percentile of placebo subjects at the same time point and based on prior SARS-CoV-2 exposure) along with 95% CIs based on the Clopper-Pearson method will be summarized by study vaccine group at each post-vaccination study visit.

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

Immunogenicity analysis of available data on 1 or more serological assays at Day 0 and 1 or more additional post-vaccination time points will be performed concurrently with the official endpoint-driven efficacy analysis, and at the end of the study; in addition, immunogenicity analysis may be performed on available data on 1 or more assays at selected Cohort Stages and/or time points, including but not limited to Days 0, 21, and 35 for Stage 1 of Cohort 1; and to Days 0, 21, 35, and 3 and 6 months after the last vaccination for both Cohorts.

7.3.3 Safety Analyses

Numbers and percentages (with 95% CIs based on the Clopper-Pearson method) of subjects with solicited local and systemic AEs through 7 days after each vaccination will be summarized by study 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 study vaccine group.

Unsolicited AEs will be coded by preferred term and system organ class using the latest version of MedDRA and summarized by study vaccine group as well as by severity and relationship to study vaccine. AEs through 35 days after first vaccination; all MAAEs related to vaccine, SAE, or AESI through EOS will be listed separately and summarized by study vaccine group.

Vital sign measurements will be summarized by study vaccine group using descriptive statistics at baseline and following vaccination.

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

Safety analysis of available data through 1 or more post-vaccination time points will be performed concurrently with the official endpoint-driven efficacy analysis, and at the end of the study; in addition, safety analysis may be performed on available data on 1 or more Cohort Stages and/or time points, including but not limited to Days 0, 21, and 35 for Stage 1 of Cohort 1; and Days 0, 21, 35, and 3 and 6 months after the last vaccination for both Cohorts.

7.4 HANDLING OF MISSING DATA

For calculating geometric means and GMFR, immunogenicity values reported as below the lower level of quantification (LLOQ) will be replaced by $0.5 \times \text{LLOQ}$. Values that are greater than the upper level of quantitation (ULOQ) will be replaced by the ULOQ. Missing results will not be imputed.

7.5 PLANNED ANALYSES PRIOR TO STUDY COMPLETION

The SMC will be provided analysis data on an ongoing basis for confirming success and to review safety as the study progresses. The SMC charter and the SAP will outline the sequential nature of these reviews.

8. REFERENCE LIST

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9. APPENDICES

9.1 APPENDIX 1: LIST OF ABBREVIATIONS

Abbreviation	Term
ACE2	Angiotensin-converting enzyme 2
AE	Adverse event
AESI	Adverse event(s) of special interest
Anti-N	Anti-nucleocapsid
BMI	Body mass index
BP	Blood pressure
CABG	Coronary artery bypass graft surgery
CFR	Code of Federal Regulations
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
EBOV GP	Ebolavirus glycoprotein
eCRF	Electronic case report form
EDC	Electronic data capture
ELISA	Enzyme-linked immunosorbent assay
EOS	End of study
FDA	United States Food and Drug Administration
FLU-PRO	The InFLUenza Patient-Reported Outcome (questionnaire)
GCP	Good Clinical Practice
GMEU	Geometric mean ELISA unit
GMFR	Geometric mean fold rise
GMT	Geometric mean titer
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HAART	Highly active antiretroviral therapy
HIV	Human immunodeficiency virus
HREC	Human research ethics committee
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICS	Inhaled corticosteroids

Abbreviation	Term
ID	Identification
IgG	Immunoglobulin G
IM	Intramuscular
IRT	Interactive Response Technology
ITT	Intent-to-treat
ITT-EFF	ITT efficacy
ITT-IMM	ITT immunogenicity
IV	Intravenous
LABA	Long-acting beta2-agonist
LLOQ	Lower limit of quantification
LTRA	Leukotriene receptor antagonist
LRTI	Lower respiratory tract illness
MAAE	Medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
OTC	Over-the-counter
PCR	Polymerase chain reaction
PIMMC	Potential immune-mediated medical conditions
PP	Per-protocol
PP-EFF	PP efficacy
PP-IMM	PP immunogenicity
RMPRU	Respiratory and Meningeal Pathogens Research Unit
RR	Relative risk
RSV F	Respiratory syncytial virus fusion (protein)
S	Spike (protein)
SABA	Short-acting beta2-agonist
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV	Severe acute respiratory syndrome coronavirus
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SARS-CoV-2 rS	SARS-CoV-2 recombinant spike (S) protein nanoparticle vaccine
SCR	Seroconversion rate
Sf9	<i>Spodoptera frugiperda</i> (insect cells)
SMC	Safety Monitoring Committee
SOE	Schedule of Events

Abbreviation	Term
SRR	Seroresponse rate
ULOQ	Upper limit of quantitation
US	United States
VE	Vaccine efficacy

9.2 APPENDIX 2: STUDY GOVERNANCE

9.2.1 Data Quality Assurance

This study will be conducted using the quality processes described in applicable procedural documents. The quality management approach to be implemented will be documented and will comply with current International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidance on quality and risk management. All aspects of the study will be monitored for compliance with applicable government regulatory requirements, current Good Clinical Practice (GCP), the protocol, and standard operating procedures. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and personnel. eCRFs and EDC will be utilized. The EDC system is validated and compliant with US Title 21 Code of Federal Regulations (CFR) Part 11 and local regulations. Each person involved with the study will have an individual identification code and password that allows for record traceability.

Important protocol deviations, should they occur during the study, will be presented in Section 10.2 of the clinical study report.

9.2.2 Investigator Obligations

The following administrative items are meant to guide the investigator in the conduct of the study and may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the HREC but will not result in protocol amendments.

9.2.2.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject, except as necessary for monitoring and auditing by the sponsor, its designee, relevant regulatory authority(ies), or the HREC.

The investigator and all employees and co-workers involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

9.2.2.2 Institutional Review

Prior to initiation of a study site, regulatory authority regulations and the ICH E6(R2) guidelines require that approval be obtained from an HREC before participation of human subjects in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study subjects, and any other written information regarding this study to be provided to the subject must be approved by the HREC. Documentation of all HREC approvals and of the HREC compliance with the ICH E6(R2) guidelines will be maintained by the study site and will be available for review by the sponsor or its designee.

All HREC approvals should be signed by the HREC chairman or designee and must identify the HREC name and address, the clinical protocol by title or protocol number or both and the date approval or a favorable opinion was granted.

9.2.2.3 Subject Consent

Written informed consent in compliance with US Title 21 CFR Part 50 and local regulatory authority requirements shall be obtained from each subject before he or she enters the study or before any unusual or nonroutine procedure that involves risk to the subject is performed. If any institution-specific modifications to study-related procedures are proposed or made by the study site, the consent should be reviewed by the sponsor or its designee or both before HREC submission. Once reviewed, the investigator will submit the ICF to the HREC for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating subjects must sign the revised form.

Before recruitment and enrolment, each prospective subject will be given a full explanation of the study and be allowed to read the approved ICF. Once the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give his or her consent to participate in the study by signing the ICF.

The investigator or designee will provide a copy of the ICF to the subject. The original form shall be maintained in the subject's medical records at the study site.

9.2.2.4 Study Reporting Requirements

By participating in this study, the investigator agrees to submit reports of SAEs according to the timeline and method outlined in this protocol. In addition, the investigator agrees to submit annual reports to his or her HREC as appropriate.

9.2.2.5 Financial Disclosure and Obligations

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 PPD 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 PPD nor the study site is financially responsible for further treatment of the disease under study.

9.2.2.6 Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6(R2) Section 8.2, US Title 21 of the CFR, and local regulations by providing essential documents, including but not limited to, the following:

- HREC approval.
- An original investigator-signed investigator agreement page of the protocol.
- Curriculum vitae for the principal investigator and each sub-investigator. Current licensure must be noted on the curriculum vitae. They will be signed and dated by the principal investigators and sub-investigators at study start-up, indicating that they are accurate and current.
- Financial disclosure information to allow the sponsor to submit complete and accurate certification or disclosure statements required under US Title 21 CFR Part 54 and local regulations. In addition, the investigators 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 after the completion of the study.
- An HREC-approved ICF, samples of study site advertisements for recruitment for this study, and any other written information about this study that is to be provided to the subject.
- Laboratory certifications and reference ranges for any local laboratories used by the study site, in accordance with US Title 42 CFR Part 493 and local regulations.

9.2.2.7 Study Conduct

The investigator agrees that the study will be conducted according to the principles of ICH E6(R2). The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. The study will be conducted in compliance with the protocol, current GCP guidelines – adopting the principles of the Declaration of Helsinki – and all applicable regulatory requirements.

Prior to study initiation, the protocol and the informed consent documents will be reviewed and approved by the sponsor and an appropriate ethics committee. Any amendment to the protocol or consent materials must also be approved by the study sponsor and HREC and must be submitted, notified, or approved to the regulatory authority, as required, before they are implemented.

9.2.2.8 Case Report Forms and Source Documents

Site personnel will maintain source documentation, enter subject data into the eCRF as accurately as possible, and will rapidly respond to any reported discrepancies.

eCRFs and EDC will be utilized. The EDC system is validated and compliant with US Title 21 CFR Part 11 and local regulations. Each person involved with the study will have an individual identification code and password that allows for record traceability. Thus, the system, and any subsequent investigative reviews, can identify coordinators, investigators, and individuals who have entered or modified records, as well as the time and date of any modifications. There may be an internal quality review audit of the data and additional reviews by the clinical monitor.

Each eCRF is presented as an electronic copy, allowing data entry by site personnel, who can add and edit data, add new subjects, identify and resolve discrepancies, and view records. This system provides immediate direct data transfer to the database, as well as immediate detection of discrepancies, enabling site coordinators to resolve and manage discrepancies in a timely manner.

Paper copies of the eCRFs and other database reports may be printed and signed by the investigator. This system provides site personnel, monitors, and reviewers with access to hardcopy audits, discrepancy reviews, and investigator comment information.

9.2.2.9 Adherence to Protocol

The investigator agrees to conduct the study as outlined in this protocol, in accordance with ICH E6(R2) and all applicable guidelines and regulations.

9.2.2.10 Reporting Adverse Events

By participating in this study, the investigator agrees to submit reports of SAEs according to the timeline and method outlined in this protocol. In addition, the investigator agrees to submit annual reports to his or her HREC as appropriate. The investigator also agrees to provide the sponsor with an adequate report, if applicable, shortly after completion of the investigator's participation in the study.

9.2.2.11 Investigator's Final Report

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the HREC with a summary of the study's outcome and the sponsor and regulatory authority(ies) with any reports as required. Interim reports are expected to be provided to regulatory authorities to allow vaccine development advancement given the pandemic situation. These reports are planned to be aggregate and at the vaccine level unless the SMC deems additional data at the individual level (eg, select listings of select subjects) will be beneficial. In such a case, a firewall will be in place to maintain the blind for those individuals involved in the study conduct to ensure unbiased assessment continue.

9.2.2.12 Records Retention

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 study 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.

9.2.2.13 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the sponsor will be responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and any other related issues. The sponsor has final approval authority over all such issues.

Data are the property of the sponsor and cannot be published without their prior authorization, but data and any publication thereof will not be unduly withheld.

9.2.3 Study Management

9.2.3.1 Monitoring

9.2.3.1.1 Monitoring of the Study

The clinical monitor, as a representative of the sponsor, is obligated to follow the study closely. In doing so, the monitor will visit the investigator and study site at periodic intervals in addition to maintaining necessary telephone and email contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and personnel. The monitor will be blinded to vaccine assignment. A separate unblinded study monitor will be responsible for drug accountability.

All aspects of the study will be carefully monitored by the sponsor or its designee for compliance with applicable government regulation with respect to current ICH E6(R2) guidelines and standard operating procedures.

9.2.3.1.2 Inspection of Records

The investigator and institution involved in the study will permit study-related monitoring, audits, HREC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the sponsor, their representatives, or the regulatory authority access to all study records.

The investigator should promptly notify the sponsor of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

9.2.3.2 Management of Protocol Amendments and Deviations

9.2.3.2.1 Modification of the Protocol

This is a Phase 2a/b study to evaluate the safety and immunogenicity of SARS-CoV-2 rS with Matrix-M1 adjuvant. This protocol is written with some flexibility to accommodate the evolving pandemic and urgency for efficacious vaccine availability. Modifications to the dose, dosing regimen, and/or clinical or laboratory procedures currently outlined below may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study subjects:

- The timing of procedures for assessment of safety procedures may be modified based on newly available safety and tolerability data or evolving COVID-19 data.

- Up to an additional 25 mL of blood may be drawn for safety or immunogenicity analyses. The total blood volume withdrawn from any single subject will not exceed the maximum allowable volume during his or her participation in the entire study.
- Additional database freezes may occur as the study evolves and should the ongoing epidemic progression warrant rapid decision-making on product manufacturing. The study will continue in a blinded fashion (at the subject level) until the EOS.
- Rapid diagnostic testing for SARS-CoV-2 by point-of-care tests may be available and substituted for centralized testing if accepted by regulatory authorities as a secondary endpoint in this study and hold validity for vaccine advancement.

It is understood that the current study may employ some or none of the alterations described above. Any changes in this research activity, except those necessary to remove an apparent immediate hazard to the subject, must be reviewed and approved by the sponsor or designee. Amendments to the protocol must be approved by the HREC, and regulatory authority where applicable, before subjects can be enrolled into an amended protocol.

9.2.3.2.2 Protocol Deviations

The investigator or designee must document and explain in the subject's source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change to, the protocol to eliminate an immediate hazard to study subjects without prior HREC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the HREC for review and approval, to the sponsor for agreement, and to the regulatory authorities, if required.

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol. An important deviation (sometimes referred to as a major or significant deviation) is a subset of protocol deviations that leads to a subject being discontinued from the study or significantly affects the subject's rights, safety, or well-being and/or the completeness, accuracy, and reliability of the study data. An important deviation can include nonadherence to inclusion or exclusion criteria or nonadherence to regulatory authority including ICH E6(R2) guidelines.

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. The investigator will be notified in writing by the monitor of deviations. The HREC should be notified of all protocol deviations, if appropriate, in a timely manner.

9.2.3.3 Study Termination

Although the sponsor has every intention of completing the study, they reserve the right to discontinue it at any time for clinical or administrative reasons.

The end of the study is defined as the date on which the last subject completes the last study visit (including the EOS visit and any additional long-term follow-up). 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.

9.2.3.4 Final Report

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.

9.3 APPENDIX 3: FDA TOXICITY GRADING SCALES

Table 9-1 FDA Toxicity Grading Scale for Clinical Abnormalities (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](#).

Table 9-2 FDA Toxicity Grading Scale for Clinical Abnormalities (Vital Signs)

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

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

Note: Subject should be at rest for all vital sign measurements, with toxicity scored on day of vaccination (pre- and post-dose).

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

Source: [DHHS 2007](#).

9.4 APPENDIX 4: 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 in [Table 9-3](#). 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 investigational products 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 9-3 Potential Immune-Mediated Medical Conditions (PIMMC)

Categories	Diagnoses (as MedDRA Preferred Terms)
Neuro-inflammatory Disorders:	Acute disseminated encephalomyelitis (including site specific variants: eg, noninfectious 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
Vasculidities:	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 anti-neutrophil cytoplasmic antibody [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
Skin Disorders:	Alopecia areata, psoriasis, vitiligo, Raynaud’s phenomenon, erythema nodosum, autoimmune bullous skin diseases (including pemphigus,

Categories	Diagnoses (as MedDRA Preferred Terms)
	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, 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.	
^a For Hashimoto thyroiditis: new onset only.	

AESIs relevant to COVID-19 are listed in [Table 9-4](#). The list is not intended to be exhaustive, nor does it exclude the possibility that other diagnoses may be AESI. It is anticipated that additional AESI may be associated with COVID-19. Investigators should stay updated regarding such public health notifications.

Table 9-4 Adverse Events of Special Interest Relevant to COVID-19

Body System	Diagnoses ^a
Immunologic	Enhanced disease following immunization, cytokine release syndrome related to COVID-19 ^b , Multisystem inflammatory syndrome in children (MIS-C)
Respiratory	Acute respiratory distress syndrome (ARDS)
Cardiac	Acute cardiac injury including: <ul style="list-style-type: none"> • Microangiopathy • Heart failure and cardiogenic shock • Stress cardiomyopathy • Coronary artery disease • Arrhythmia • Myocarditis, pericarditis
Hematologic	Coagulation disorder <ul style="list-style-type: none"> • Deep vein thrombosis • Pulmonary embolus • Cerebrovascular stroke • Limb ischemia • Hemorrhagic disease • Thrombotic complications
Renal	Acute kidney injury
Gastrointestinal	Liver injury
Neurologic	Guillain-Barré Syndrome, anosmia, ageusia, meningoencephalitis
Dermatologic	Chilblain-like lesions, single organ cutaneous vasculitis, erythema multiforme

Abbreviations: COVID-19 = coronavirus disease 2019; DAIDS = Division of AIDS.

^a COVID-19 manifestations associated with more severe presentation and decompensation with consideration of enhanced disease potential ([SPEAC 2020](#)).

^b 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](#)).