Project Brief: NVX2019nCOV501

Full Title of Study/Programme	A phase 2A/B, randomized, observer-blinded, placebocontrolled 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
Technical Focus Area	Research (Adults)
Rationale	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).
Primary Objectives(1/2)	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.
Secondary Objectives (1/2)	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 SARSCoV-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
Primary Objectives(2/2)	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)
Secondary Objectives (2/2)	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.
Primary Endpoint/Outcome Cohort 1 HIV Negative	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. (+) 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. 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
Secondary Objective (Cohort 1)	(+) 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 ≥ 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
Primary Objection (Cohort 2)	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.
Secondary Objectives(Cohort 2)	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 ≥ 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 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 (≥ 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.
Study Design (R)	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. 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)
Study arms (R)	1. Healthy HIV-negative adult male or nonpregnant female subjects (Cohort 1) 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.
Study population (R)	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.
Study sample size (R)	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
Follow up/duration	Study Participants will be followed -up for 1 year
Study/Programme sites	WITS RHI RMPRU PHRU Setchaba Research Centre CAPRISA Madibeng Research Centre

Study/Programme duration	The total duration of the study will be 12 months from the day of enrolment for all participants.
Investigators	Prof Lee Fairlie, Principal Investigator Dr Gabrielle Benade,, co-Principal Investigator Dr Faeezah Patel, Sub Investigator Dr Masebole Masenya, Sub Investigator Dr Elizea Horne, Sub-Investigator Dr Alden Nicholas Geldenhuys, Sub Investigator Dr Mrinmayee Dhar, Sub Investigator
Other Partners & Collaborators	
Sponsors/Donors	Novavax Inc
Publications/key presentations to date	
Progress Update as at Oct 2020	Enrolled: 379(2 withdrew consent before vaccination) On Study: 375 Withdrawal: 02
Frequency of donor narrative report	
Overall Study/Project Contact	Dr Hermien Gous (hgous@wrhi.ac.za)
Briefing owner and date	Dr Hermien Gous 20 Oct 2020 Dr Gabriella Benade Dr Lee Fairlie