Project Brief: 2019nCoV-505

Full Title of Study/Programme	A Phase 2, Randomized, Observer-Blinded Study to Evaluate the Safety and Immunogenicity of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine (SARS-CoV-2 rS) with Matrix-M™Adjuvant in People Living with HIV
Technical Focus Area/Key Words	Phase 2 Study of the Safety and Immunogenicity of a COVID-19 Vaccine in People Living with HIV
Rationale	Novavax, Inc. is developing recombinant vaccines adjuvanted with the saponin-based Matrix-M adjuvant for the prevention of disease caused by SARS-CoV-2. Both nonclinical and clinical data to date support continued clinical development of SARS-CoV-2 recombinant (r) spike (S) protein nanoparticle vaccines (SARS-CoV-2 rS) combined with Matrix-M adjuvant as potential vaccines against SARS-CoV-2. Reports from the United Kingdom (UK), Brazil, South Africa, and India revealed the emergence of the B.1.1.7 (Alpha), P.1 (Gamma), B.1.351 (Beta), and B.1.617.2 (Delta) variants of SARS-CoV-2, respectively, with confirmed acquisition of mutations in key antigenic sites in the receptor binding domain (RBD) and N-terminal domain of the S protein. For the prototype SARS-CoV-2 rS with Matrix-M adjuvant, clinical efficacy results are available from studies run in the UK and South Africa where some of these variants have circulated. In the UK study, the overall efficacy of the vaccine was 89.7% (95% confidence interval [CI]: 80.2, 94.6) and, in post hoc analyses, efficacy estimates for the B.1.1.7 (Alpha) variant and for the ancestral strain were 86.3% and 96.4%, respectively. In the South Africa study, the efficacy of the vaccine in all study participants was 48.6% (95% CI: 28.4, 63.1) and 55.4% (95% CI: 35.9, 68.9) in participants who were HIV-negative. The efficacy estimates in South Africa were generated in a period of > 90% B.1.351 (Beta) variant virus circulation. Novavax, in partnership with the SII, has undertaken the production of rS nanoparticle vaccines using the sequenced genomes from the prototype virus and of the B.1.351 (Beta) and B.1.617.2 (Delta) variants. SII employs a vaccine production process consistent with that used at Novavax, and like Novavax-produced products, the vaccines are intended for administration with Matrix-M adjuvant, which is a saponin-based adjuvant that has previously been shown to enhance the immunogenicity of other nanoparticle vaccines in nonclinical and clinical studies. In the ongoing 4,400-person Phase 2a/b study of NVX-CoV2373 (5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant) in South Africa, 245 (~5%) randomly assigned participants were PLWH. Due to a difference in the immune response mounted between baseline seropositive and seronegative (to SARS-CoV2) PLWH in that study, we hypothesize for this study that an expanded interval between vaccinations or an additional immunizing exposure to vaccine may establish an optimal vaccine regimen that would allow PLWH to mount an immune response comparable to that seen for HIV-negative adults, regardless of baseline serostatus. Following a two-dose regimen, 21 days apart, the efficacy of the vaccine in the prevention of COVID-19 of any severity in all study participants (regardless of HIV status) who were seronegative at baseline (to SARS-CoV-2) was 48.6% (95% CI: 28.4, 63.1). In participants who were HIV-negative and seronegative at baseline (to SARS-CoV-2), vaccine efficacy was 55.4% (95% CI: 35.9, 68.9). Although the study was not powered to estimate efficacy among the small cohort of PLWH, no efficacy was detected in this group. Notably, endpoint cases in the Phase 2b study in South Africa were collected during a time

	period in which > 90% of all COVID19 disease in South Africa was caused by the Beta variant. Immunogenicity analysis of immunoglobulin G (IgG) antibody in the vaccine group of HIV-negative participants who were seronegative at baseline (to SARS-CoV-2), showed Day 0 geometric mean titer (GMT) of 111 enzyme-linked immunosorbent assay (ELISA) units (EU)/mL (95% CI: 109, 114). The GMT rose at Day 21 to 1,195 EU/mL (95% CI: 1,117, 1280) representing an 81.3% 4-fold seroconversion rate (SCR) and at Day 35, it was 31, 632 EU/mL (95% CI: 29,713, 33,675), representing a 99.3% 4-fold SCR. Immunogenicity analysis of IgG antibody in the vaccine group of PLWH who were seronegative at baseline, showed Day 0 GMT of 116 EU/mL (95% CI: 104, 129). The GMT rose at Day 21 to 508.6 EU/mL (95% CI: 382, 677), representing a 51.6% 4-fold SCR, and at Day 35, GMT was 14,421 EU/mL (95% CI: 10,603, 19,612), representing a 100% 4-fold SCR. The rise in GMT seen in the PLWH who were seronegative at baseline (to SARS-CoV-2), was approximately half of that observed in HIV-negative counterparts. In the participants who were seropositive at baseline, immunogenicity analysis of IgG antibody in the vaccine group of HIV-negative participants, showed Day 0 GMT of 1,713 EU/mL (95% CI: 1,536, 1,910). The GMT rose at Day 21 to 21,138 EU/mL (95% CI: 18,571, 24,059) representing an 82.2% 4-fold SCR and at Day 35, it was 100,666 EU/mL (95% CI: 92,996, 108,969), representing a 97.3% 4-fold SCR. In PLWH, immunogenicity analysis of IgG antibody in the vaccine group showed Day 0 GMT of 1,853 EU/mL (95% CI: 1,195, 2,872). The GMT rose at Day 21 to 19,240 EU/mL (95% CI:9,825, 37,678) representing a 74.4% 4-fold SCR, and at Day 35, GMT was 98,400 (95% CI: 61,857, 156,530), representing a 92.3% 4-fold SCR. The SCR and rise in GMT seen in the PLWH who were seropositive at baseline (to SARS-CoV-2), is comparable to what was observed in HIV-negative counterparts, suggesting that prior exposure to the virus and the development of seropositivity at baseline, eliminates the difference in observable immune response between HIV-negative adults and PLWH. Across all clinical studies conducted to date, the NVX-CoV2373 vaccine has continued to demonstrate good tolerability and an acceptable safety profile. The purpose of this safety and immunogenicity study is to determine an optimal regimen/dosing interval for PLWH aged 18 to 65 years across a spectrum of baseline control of HIV-infection as indicated by baseline level of control of HIV infection. Stratification by level of control of HIV viral infection will be used to achieve balance in the treatment groups.
Primary Objectives	• To describe the amplitude, kinetics, and durability of immune response to NVX-CoV2373 in terms of ELISA units of serum IgG antibodies, titers of neutralizing antibody, and titers of human angiotensin-converting enzyme 2 (hACE2) receptor binding inhibition activity assayed in a system using the SARS-CoV-2 rS protein(s) (reflecting the amino acid sequence of that of the prototype virus) at selected time points, stratified by baseline HIV status and in PLWH, stratified by level of control of HIV infection into well-controlled and lesswell-controlled treatment groups. To include reverse cumulative distribution (RCD) curves. • To assess overall safety through Day 84 after initial vaccination for all unsolicited adverse events (AEs) and all medically attended adverse events (MAAEs); and safety through Days 120 and 180 (EoS) following vaccination for any MAAE attributed to vaccine, adverse event(s) of special interest (AESIs), or serious adverse event (SAEs). • To accumulate and describe the safety experience for NVX-CoV2373 based on solicited short-term reactogenicity (by toxicity grade) and by AE profile for vaccination through Day 84 in PLWH and HIV-negative adult participants and, in PLWH, stratified by level of control of HIV infection into well-controlled and less-well-controlled treatment groups.

Secondary Objectives	To describe the difference in amplitude, kinetics, and durability of immune response in terms of ELISA units of serum IgG antibodies and titers of hACE2 receptor binding inhibition assayed with the SARS-CoV-2 rS protein(s) (reflecting the amino acid sequence of that of the prototype virus) at selected time points between HIV-negative participants receiving either a two- or three-dose vaccination regimen. To include RCD curves.
Exploratory Objectives	To describe the cellular immune response as measured by intracellular cytokine staining (ICCS) and assay for interleukin 2 (IL-2), tumor necrosis factor alpha (TNFα), and interferon gamma (IFNγ) to a primary two-dose or three-dose regimen of NVX-CoV2373 in terms of antigen-specific CD4+ T-cell responses in peripheral blood mononuclear cells (PBMCs) at selected study time points in PLWH and HIV-negative adult participants (with PLWH stratified by level of control of HIV infection into well-controlled and less-well-controlled treatment groups)
Study Design (R)	This is a Phase 2, randomized, observer-blinded study evaluating the safety and immunogenicity of novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine construct adjuvanted with Matrix-M adjuvant in people living with human immunodeficiency virus (HIV) (PLWH) and HIV-negative adults, seronegative to SARS-CoV-2 at baseline. The investigational product will be a monovalent Serum Institute of India (SII) SARS-CoV-2 vaccine at a dose of 5 µg antigen adjuvanted with 50 µg Matrix-M (referred hereafter as NVX-CoV2373). Approximately 270 PLWH, 18 to 65 years of age inclusive, will be enrolled into 3 groups and stratified at presentation based on the level of control of HIV infection (as determined by viral load [≤ 1,000 copies/mL vs 1,000 to 10,000 copies/mL and CD4+ T-cell count [≥ 350 cells/µL vs ≥ 200 and < 350 cells/µL] to distribute well-controlled [viral load: ≤ 1,000 copies/mL; CD4+ T-cell count: ≥ 350 cells/µL] and less-well-controlled [viral load: 1,000 to 10,000 copies/mL; CD4+ T-cell count: ≥ 200 and < 350 cells/µL], receipt of stable antiretroviral therapy regimen, and presence of opportunistic infections) so that the distribution in all treatment groups reflects the population presenting for study. All PLWH will be baseline seronegative (for SARS-CoV-2). PLWH will be randomly assigned 1:1:1 to receive NVX-CoV2373 in either a two-dose regimen on Days 0 and 21 or Days 0 and 70 or a three-dose regimen on Days 0, 21, and 70. Randomization of PLWH will be stratified by level of control of HIV infection to distribute well-controlled and less-well-controlled participants approximately evenly among the 3 PLWH treatment groups. Approximately 90 HIV-negative participants, 18 to 65 years of age inclusive, will be randomly assigned 1:1 to receive NVX-CoV2373 in a two-dose regimen on Days 0 and 21 or Days 0 and 70. All HIV-negative participants will be baseline seronegative (for SARS-CoV-2). Placebo (normal saline solution) will be administered to participants who receive a two-dose regimen of NVX-CoV2373 to maintain overall blinding. All participants, following vaccination, will remain on study for immunogenicity and safety data collection through Day 180 (End of Study [EoS])

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<tr><td>Study arms (R)</td><td>
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<tr><th>Group</th><th>Day 0</th><th>Day 21</th><th>Day 70</th><th>N</th></tr>
<tr><td>1 PLWH</td><td>NVX-CoV2373</td><td>NVX-CoV2373</td><td>Placebo</td><td>90</td></tr>
<tr><td>2 PLWH</td><td>NVX-CoV2373</td><td>NVX-CoV2373</td><td>NVX-CoV2373</td><td>90</td></tr>
<tr><td>3 PLWH</td><td>NVX-CoV2373</td><td>Placebo</td><td>NVX-CoV2373</td><td>90</td></tr>
<tr><td>4 HIV-Negative</td><td>NVX-CoV2373</td><td>NVX-CoV2373</td><td>Placebo</td><td>45</td></tr>
<tr><td>5 HIV-Negative</td><td>NVX-CoV2373</td><td>Placebo</td><td>NVX-CoV2373</td><td>45</td></tr>
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<tr><td>Study population (R)</td><td>PLWH and HIV-negative adults 18 to 65 years of age, inclusive.</td></tr>
<tr><td>Study sample size (R)</td><td>360, approximately 40 at Shandukani CRS</td></tr>
<tr><td>Follow up/duration</td><td>On study (including screening and follow-up): 180 days with vaccine administration on Days 0, 21, and 70.</td></tr>
<tr><td>Study/Programme sites</td><td>ZA003 Wits RHI Shandukani Research Centre (SRC)
ZA001
ZA018
ZA022
ZA023
ZA024
ZA028</td></tr>
<tr><td>Intervention (R)</td><td>NVX-CoV2373 is supplied as a pre-mixture solution for preparation for injection comprising SARS-CoV-2 rS (with an amino acid sequence reflecting that of the prototype virus) at a concentration of 10 µg/mL and Matrix-M adjuvant at a concentration of 100 µg/mL. The vaccination regimen will comprise either 2 intramuscular (IM) injections (Days 0 and 21 or Days 0 and 70) with placebo administered on Days 70 or 21, respectively, to maintain overall blinding) or 3 IM injections (Days 0, 21, and 70) of 0.5 mL injection volume at a dose of 5 µg antigen and 50 µg Matrix-M adjuvant.</td></tr>
<tr><td>Operations</td><td>Study specific</td></tr>
<tr><td>Investigators</td><td>Dr Faeezah Patel PI
Dr Elizea Horne
Dr Mrinmayee Dhar
Dr Robert Kieser
Tiffany Seef
Othusitse Segalo</td></tr>
<tr><td>Other Partners & Collaborators</td><td>BARC / ICON</td></tr>
<tr><td>Sponsors/Donors</td><td>Novavax</td></tr>
<tr><td>Linked Sub Studies and post grad projects</td><td>None</td></tr>
<tr><td>Publications/key presentations to date</td><td>None as yet</td></tr>
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Progress Update as at Sep-2023	Screened 72 Enrolled 36 Screen / Failures: 36 Enrolments closed Off study: 29 Study closed / COV 21-Apr-2023
Frequency of donor narrative report	
Overall Study/Project Contact	Hermien Gous
Briefing owner and date	Prof Lee Fairlie Sep-2023 Dr Hermien Gous Sep-2023