**Trial Title:** An adaptive phase I/II randomized placebo-controlled trial to determine safety, immunogenicity and efficacy of non-replicating ChAdOx1 SARS-CoV-2 vaccine in South African adults living without HIV; and safety and immunogenicity in adults living with HIV.

**Study Reference:** ChAdOx1 nCoV-19_ZA_phI/II

**Protocol Version:** South Africa version 4.1

**Date:** ZA_30th September 2020

**Trial registration**: Clinicaltrials.gov: NCT04444674;
Pan African Clinical Trial Registry: PACTR202006922165132.

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**Protocol Co-Chair (UK):** Prof Andrew Pollard
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**Sponsor:** University of Oxford

**Funder:** UK Research and Innovation (For Vaccine supply only)
Funding: The Bill and Melinda Gates Foundation
and South African Medical Research Council

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| | |
|---|---|
| **Funders** | UK Research and Innovation (Vaccine supply)<br><br>Clinical Trial: The Bill and Melinda Gates Foundation and South African Medical Research Council |
| **External Monitor, SA** | PPD SA (PTY) Ltd (blinded)<br><br>The Woodlands Office Park, Building 15,<br><br>Cnr Kelvin and Woodlands Drive, Woodmead, 2191, PO Box 37,<br><br>Woodlands, 2080<br><br>Phone: 011 612 8600<br><br>Fax: 011 612 8700<br><br>Contacts: Nicolette Stott; Nicolette.stott@ppdi.com<br><br>Savi Chetty-Tulsee (Unblinded, regulatory)<br>SCT consulting<br>Bryanston Homesteads, Ben Road, Bryanston, 2191<br>Email: savi.sct@mweb.co.za |

# Contents

# Table of tables

# Investigator agreement

The principal investigator is responsible for ensuring that all study site personnel, including sub-investigators and other staff members, conduct this trial according to this protocol, Good Clinical Practice (GCP) and International Conference on Harmonization (ICF) guidelines, the Declaration of Helsinki and the pertinent country laws and regulations and to comply with its obligations, subject to ethical and safety considerations during and after the trial completion. The principal investigator also agrees not to disclose the information contained in this protocol or any results obtained from this trial without written authorization.

I have read and approve the protocol specified above and agree in its content:

| | |
|---|---|
| Role: National Principal Investigator, Protocol co-chair | Name: Shabir A. Madhi |
| Signature: DocuSigned by: [redacted] 1E5B1570B94F452... | Date: 10/1/2020 |

| | |
|---|---|
| Role: Protocol co-chair, University of Oxford | Name: Andrew Pollard |
| Signature: DocuSigned by: [redacted] | Date: 10/1/2020 |

| | |
|---|---|
| Role: VIDA/ RMPRU site Principal Investigator | Name: Anthonet Koen |
| Signature: DocuSigned by: [redacted] 46C683D57BD3476... | Date: 10/1/2020 |

| | |
|---|---|
| Role: Wits RHI Shandukani Research Centre Principal Investigator | Name: Lee Fairlie |
| Signature: DocuSigned by: [redacted] 5532C86B99CA426... | Date: 10/1/2020 |

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| Role: Setshaba Research Centre Principal Investigator | Name: Sherman D. Padayachee |
| Signature: DocuSigned by: [redacted] E3EF5A4AE765460... | Date: 10/1/2020 |

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|---|---|
| Role: PHRU Klipto[illegible] Principal Investigator | Name: Carmen Briner |
| Signature: [redacted] A2ECFCE0D904430... | Date: 10/1/2020 |

| | |
|---|---|
| Role: FAMCRU Principal Investigator | Name: Shaun Barnabas |
| Signature: DocuSigned by: [redacted] 6281F30D44094AE... | Date: 10/1/2020 |

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| Role: UCT CLII Principal Investigator | Name: Prof Keertan Dheda |
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|---|---|
| Role: SCTC Principal Investigator | Name: Dr Qasim Bhorat |
| Signature: DocuSigned by: [redacted] 696269FC4D1A423... | Date: 10/1/2020 |

# 1. SYNOPSIS

| | |
|---|---|
| **Trial Title** | An adaptive phase I/II randomized placebo-controlled trial to determine safety, immunogenicity and efficacy of non-replicating ChAdOx1 SARS-CoV-2 vaccine in South African adults living without HIV; and safety and immunogenicity in adults living with HIV |
| **Trial Identifier** | ChAdOx1 nCoV-19_ZA_phI/II |
| **Trial Registration** | Clinicaltrials.gov: NCT04444674;<br>Pan African Clinical Trial Registry: PACTR202006922165132 |
| **National Principal investigator and Protocol Co-chair, South Africa** | Professor Shabir A. Madhi |
| **UK Protocol Co-chair** | Professor Andrew Pollard |

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| **Clinical Phase** | I/II |
| **Design** | Double -blinded, randomised, placebo controlled, multi-centre |
| **Population** | Healthy adults aged 18-65 years, living with and without HIV |
| **Planned Sample Size** | **2070** (possible upward adjustment for efficacy endpoint) |
| **Planned Trial Duration:** | Regular visits from enrolment through to at least 12 months later. |

*Summary table of groups*

| Group # | Group description | Objective | Follow up | Treatment | Vaccination schedule |
|---|---|---|---|---|---|
| 1 (n=70) | People without HIV (HIV-uninfected) | Intensive Safety and immunogenicity | Intensive | ChAdOx1 nCoV-19 5-7.5x1010 vp; OR Normal saline (0.9% NaCl) | 2* doses, 4 weeks (21-35 days) apart |
| 2a (n=250) [§] | People without HIV (HIV-uninfected) | Safety, intensive immunogenicity and vaccine efficacy | Extended | ChAdOx1 nCoV-19 5-7.5x$10^{10}$ vp; OR Normal saline (0.9% NaCl) | 2* doses, 4 weeks (21-35 days) apart |
| 2b (n=1650) [§] | People without HIV (HIV-uninfected) | Safety, immunogenicity and vaccine efficacy | Extended | ChAdOx1 nCoV-19 5-7.5x$10^{10}$ vp; OR Normal saline (0.9% NaCl) | 2* doses, 4 weeks (21-35 days) apart |
| 3 (n=100) | People living with HIV (HIV-infected) | Intensive Safety and immunogenicity | Intensive | ChAdOx1 nCoV-19 5-7.5x$10^{10}$ vp; OR Normal saline (0.9% NaCl) | Prime-boost 2* doses, 4 weeks (21-35 days) apart |

*Participants will receive 2 doses of the same injection (EITHER IP or placebo) as assigned at randomization.

[§]Numbers will be increased to supplement for corresponding number of individuals randomized prior to implementation of Version 3.0 of the protocol that tested positive for SARS-CoV-2 on PCR at time of randomization.

[#] Following review of the initial safety/immunogenicity phase I trial conducted in the UK; COV0001 trial, and after review of the initial safety/ immunogenicity trial COV0001 by the DSMC; it was confirmed that Group 2 participants will receive 2 doses. SAHPRA and WHREC had been informed of this decision based on the earlier protocol requirements. Also, considering the unpredictability of the force of SARS-CoV-2 infection and the lower than anticipated attack rate for the primary-endpoint cases in the study being undertaken in the UK, the sample size for Group 2 (efficacy cohort) was expanded from the 550 included in protocol version 1.0, dated 24th April 2020. This will involve enrolling up to a total of 1900 people in Group-2, which will provide 80% power to detect at least a 60% vaccine efficacy (lower bound of 95%CI >0) with an attack rate of 3.5% in the placebo arm. Ongoing review of the number of COVID-19 endpoint cases accrued during the course of the study, may lend itself to enrolling smaller number of participants should the attack rate be higher than 3.5%. The sample size for Group-1 has been increased to 70 to accommodate for the higher than anticipated infection rate with SARS-CoV-2 (6 of initial 24 randomized subjects in Group-1). Similarly, in anticipation of approximately one-third of Group-3 participants possibly being already infected with SARS-CoV-2, the sample size will be increased to 100 to have approximately 30 sero-negative vaccinees and placebo recipients enrolled into the study.

*Visit schedule, group 1 and 3*

| Visit number | Screening | V1 | V2 | V3 | V4 | V5 | V6* | V7* | V8* | V9* | V10 | V11 | COVID-19 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Day # | -14 to -1 | 0 (Vax1) | 3 | 7 | 14 | 28 (Vax2) | 31 | 35 | 42 | 56 | 182 | 364 | Illness |
| | Screening | D0 | V1+ 3 days ±1; (day 2-4) | V1 +7 days ±2 (day 5-9) | V1+ 14 days ±3 (day 11-17) | Visit 1 + 28 days ±7 (day 21-35) | V5+3 days ±1 | V5+7 days ±2 | V5+14 days ±3 | V5 +28 (±7) | D182 (±14) | D364 (±14 days) | As required [$] |
| Eligibility | X | X | | | | | | | | | | | |
| Consenting | X[§] | X[¥] | | | | | | | | | | | |
| Inclusion/ exclusion | X | X | | | | X | | | | | | | |
| Contraindications | X | X | | | | X | | | | | | | |
| Vital signs [#] | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Medical history | X | | | | | | | | | | | | X |
| Physical examination | X (full) | X | X | X | X | X (full) | X | X | X | X | X | X | X (full) |
| Vaccination | | X | | | | X | | | | | | | |
| Post-vaccination obs | | X | X (deltoid) | X (deltoid) | | X | X (deltoid) | X (deltoid) | | | | | |
| Diary cards provided | | X | | | | X | | | | | | | X (illness DC) |
| DC collected | | | | X | | | | X | | | | | |
| Safety bloods (FBC, U&E, LFT) | X | | X | X | | X | | X | | X | | | |
| Screening bloods (HBsAg, HIV, HbA1C) | X | | | | | | | | | | | X (HIV Gr 1) | |
| HIV Viral load and CD4 (Grp 3 only) | VL and CD4 | | | | | | | | | | | | |
| Immunology bloods*** | | E, PAX (15.0-20.0ml) | Cyt, PAX (15.0 -20.0l) | | E & CMI (20-25ml) | E, N, PAX (20.0-25.0ml) | | Cyt (10-15mls) | E & N & CMI (25-30ml) | E (10-15ml) | E (10-15ml) | E & N (15-20ml) | E (10-20ml) |
| Urinalysis | X | | | | | | | | | | | | |
| Urinalysis bHCG (women only) | X | (X) | | | | X | | | | | | | |
| Nasal swab/ saliva | X (V1-96 hours) | X | | X | X | X | | X | X | X | X | X | X |

• Visit 5 to Visit 9 are scheduled relative to when the 2nd dose of vaccine/placebo (Visit 4) has been administered.
§ Screening informed consent form (ICF).
¥Full study participation informed consent form, if remain eligible after completion of screening procedures.
# Vital signs includes pulse, respiratory rate, oxygen saturation, blood pressure and temperature;
** Timeline is approximate only. Exact timings of visits relate to the day on enrolment, i.e., each visit must occur at indicated number of days after enrolment ± time window
***Abbreviations for laboratory tests: E =Elisa; Cyt= Th1 and Th2 cytokine profile; N= neutralization and/or pseudo-neutralisation assay; CMI= cell-mediated immunity assay, PAX= PAXgenes.
Blood test summary:

- Screening: Safety bloods (Full Blood Count, FBC; Urea and Electrolytes, U&E; Liver Function tests, LFT); Screening bloods (HBsAg, HIV, Glycosylated hemoglobin; HbA1c), In group 3 only- CD4+ -lymphocyte count, CD4+ & VHIV-1 viral load, VL)
- Visit 1: Immunogenicity- Elisa
- Visit 2 Safety bloods (FBC, U&E, LFT), Immunogenicity- Th1 and Th2 cytokine profile
- Visit 3 Safety bloods (FBC, U&E, LFT)
- Visit 4 Immunogenicity- Elisa & cell-mediated immunity
- Visit 5 Safety bloods (FBC, U&E, LFT), Immunogenicity- Elisa & neutralization and/or pseudo-neutralisation assay
- Visit 6 NIL
- Visit 7 Safety bloods (FBC, U&E, LFT), Immunogenicity- Th1 and Th2 cytokine profile
- Visit 8 Immunogenicity- Elisa, neutralization and/or pseudo-neutralisation assay & cell-mediated immunity
- Visit 9 Safety bloods (FBC, U&E, LFT), Immunogenicity- Elisa
- Visit 10 Immunogenicity- Elisa
- Visit 11 Immunogenicity- Elisa & neutralization and/or pseudo-neutralisation assays
- Illness visit Immunogenicity- Elisa

$ Nasal swabs/ saliva and Elisa (illness) will be repeated at Days 5-8, 12-15 and 28-35 days.

***Visit schedule, group 2a (first 250 participants)***

| Visit number | Screening | V1 | V2 | V3 | V4 | V5* | V6* | V7* | V8 | V9 | COVID-19 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Day # | -14 to -1 | 0 (Vax1) | 7 | 14 | 28 (Vax2) | 35 | 42 | 56 | 182 | 364 | Illness |
| | Screening | D0 | V1 +7 days ±2 (day 5-9) | V1+ 14 days ±3 (day 11-17) | Visit 1 + 28 days ±7 | V4+7 days ±2 | V4+14 days ±3 | V4 +28 (±7) | D182 (±14) | D364 (±14 days) | As required [$] |
| Eligibility | X | X | | | | | | | | | |
| Consenting | X[§] | X[¥] | | | | | | | | | |
| Inclusion/ exclusion | X | X | | | X | | | | | | |
| Contraindications | X | X | | | X | | | | | | |
| Vital signs [#] | X | X | X | X | X | X | X | X | X | X | X |
| Medical history | X | | | | | | | | | | X |
| Physical examination | X (full) | X | X | X | X (full) | X | X | X | X | X | X (full) |
| Vaccination | | X | | | X | | | | | | |
| Post-vaccination obs | | X | X (deltoid) | | X | X (deltoid) | | | | | |
| Diary cards provided | | X | | | X | | | | | | X (illness DC) |
| DC collected | | | X | | | X | | | | | |
| Screening bloods (HBsAg, , HIV, HbA1C) | X | | | | | | | | | X (HIV) | |
| Immunology bloods*** | | E, PAX (15.0-20.0) | Cyt, PAX (15.0 -20.0ml) | E & CMI (20-25ml) | E, N, PAX (20.0-25.0ml) | | E & N & CMI (25-30ml) | E (10-15ml) | E (10-15ml) | E & N (15-20ml) | E (10-20ml) |
| Urinalysis | X | | | | | | | | | | |
| Urinalysis bHCG (women only) | X | (X) | | | X | | | | | | |
| Nasal swab/ saliva | X (V1-96 hours) | X | X | X | X | X | X | X | X | X | X |

• Visit 5 to Visit 7 are scheduled relative to when the 2nd dose of vaccine/placebo (Visit 4) has been administered.

§ Screening informed consent form (ICF).

¥Full study participation informed consent form, if remain eligible after completion of screening procedures.

).

[#] Vital signs includes pulse, respiratory rate, oxygen saturation, blood pressure and temperature;

** Timeline is approximate only. Exact timings of visits relate to the day on enrolment, i.e., each visit must occur at indicated number of days after enrolment ± time window

***Abbreviations for laboratory tests: E=Elisa; Cyt=Th1 and Th2 cytokine profile; N=neutralization and/or pseudo-neutralisation assay; CMI= cell-mediated immunity assay.

Blood test summary:

- Screening: Screening bloods (HBsAg, HIV, HBA1C)
- Visit 1: Immunogenicity- Elisa
- Visit 2 Immunogenicity- Th1 and Th2 cytokine profile
- Visit 3 Immunogenicity- Elisa & cell-mediated immunity assay
- Visit 4 Immunogenicity- Elisa & neutralization and/or pseudo-neutralisation assay, PAX- HLA
- Visit 5 Nil
- Visit 6 Immunogenicity- Elisa, neutralization and/or pseudo-neutralisation assay & cell-mediated immunity assay
- Visit 7 Immunogenicity- Elisa
- Visit 8 Immunogenicity- Elisa
- Visit 9 Immunogenicity- Elisa & neutralization and/or pseudo-neutralisation assay
- Illness visit Immunogenicity- Elisa

[$] Nasal swabs/ saliva and Elisa (illness) will be repeated at Days 5-8, 12-15 and 28-35 days

*Visit schedule, group 2b (extended efficacy cohort; remaining 1650 participants)*

| Visit number | Screening | V1 | V2 | V3 | V4 | V5 | V6 | COVID-19 |
|---|---|---|---|---|---|---|---|---|
| Day # | -14 to -1 | 0 (Vax1) | 28 (Vax2) | 42 | 56 | 182 | 364 | Illness |
| | Screening | D0 | Visit 1 + 28 days ±7 | V2+14 days ±3 | V2 +28 (±7) | D182 (±14) | D364 (±14 days) | As required [$] |
| Eligibility | X | X | | | | | | |
| Consenting | X[§] | X[¥] | | | | | | |
| Inclusion/ exclusion | X | X | X | | | | | |
| Contraindications | X | X | X | | | | | |
| Vital signs [#] | X | X | X | X | X | X | X | X |
| Medical history | X | | | | | | | X |
| Physical examination | X(full) | X | X (full) | X | X | X | X | X (full) |
| Vaccination | | X | X | | | | | |
| Post vaccination Obs | | X | X | | | | | |
| Diary cards provided | | X | X | | | | | X (illness DC) |
| DC collected | | | X | | | | | |
| Screening bloods (HBsAg, HIV, HbA1C) | X | | | | | | X (HIV) | |
| Immunology bloods*** | | E (15-20 ml) | E, N, HLA (20-25 ml) | E & N (15-20ml) | E (10-15ml) | E (10-15ml) | E & N (15-20ml) | E (10-20ml) |
| Urinalysis | X | | | | | | | |
| Urinalysis bHCG (women only) | X | (X) | X | | | | | |
| Nasal swab/ saliva | X (V1-96 hours) | X | X | X | X | X | X | X |

[§] Screening informed consent form (ICF).

[¥] Full study participation informed consent form, if remain eligible after completion of screening procedures.

*

[#] Vital signs includes pulse, respiratory rate, oxygen saturation, blood pressure and temperature;

** Timeline is approximate only. Exact timings of visits relate to the day on enrolment, i.e., each visit must occur at indicated number of days after enrolment ± time window

***Abbreviations for laboratory tests: E=Elisa; Cyt=Th1 and Th2 cytokine profile; N=neutralization and/or pseudo-neutralisation assay; CMI=cell-mediated immunity assay.

Blood test summary:

- Screening: Screening bloods (HBsAg, HIV, HbA1C)
- Visit 1: Immunogenicity- Elisa
- Visit 2 Immunogenicity- Elisa & neutralization and/or pseudo-neutralisation assay, HLA
- Visit 3 Immunogenicity- Elisa, neutralization and/or pseudo-neutralisation assay
- Visit 4 Immunogenicity- Elisa,
- Visit 5 Immunogenicity- Elisa
- Visit 6 Immunogenicity- Elisa & neutralization and/or pseudo-neutralisation assay
- Illness visit Immunogenicity- Elisa

$ Nasal swabs/ saliva and Elisa (illness) will be repeated at Days 5-8, 12-15 and 28-35 days.

## Objectives:

***In adults without HIV (HIV-uninfected)***

**Primary objective:**

To assess the safety of the candidate vaccine ChAdOx1 nCoV-19 in healthy HIV-uninfected adults.

**Co-primary objective:**

To assess efficacy of the candidate ChAdOx1 nCoV-19 against COVID-19, defined as virologically confirmed (PCR positive) COVID-19 disease, in participants that were COVID-19 naïve at time of randomization and who received two doses of ChAdOx1 nCoV-19 or placebo. Events will be included if they occurred more than 14 days after the booster dose. "COVID-19 naïve" will be defined as sero-negative and tested negative for SARS-CoV-2 infection based on a high sensitivity serology antibody test and molecular detection testing of nasal swab, respectively

**Secondary objective**

To assess the immunogenicity of ChAdOx1 nCoV-19 in healthy HIV-uninfected adults

Details of objectives Groups 1 & 2 (HIV-uninfected):

| Objective | Objective details | Endpoint measures |
|---|---|---|
| Primary Objective (Group 1 and Group 2) | To assess the safety, tolerability and reactogenicity profile of the candidate vaccine ChAdOx1 nCoV-19 | a) occurrence of solicited local reactogenicity signs and symptoms for 7 days following vaccination;<br>b) occurrence of solicited systemic reactogenicity signs and symptoms for 7 days following vaccination;<br>c) occurrence of unsolicited adverse events (AEs) for 28 days following vaccination;<br>d) change from baseline for safety laboratory measures and;<br>e) occurrence of serious adverse events<br>e) occurrence of disease enhancement episodes |

<table>
<tr>
<td>Co- Primary objective<br><br>(Group 2a and 2b; efficacy cohort)</td>
<td>To assess efficacy of the candidate ChAdOx1 nCoV-19 against mild to severe COVID-19</td>
<td>The primary efficacy [objective] and endpoint include PCR positive COVID-19 disease cases occurring in participants that were COVID-19 naïve at the time of randomization and who received at least two doses of ChAdOx1 nCoV-19 or placebo. Events will be included if they occurred more than 14 days after the booster dose.<br>Virologically-confirmed COVID-19 clinical disease will be defined as an acute respiratory illness that is clinically consistent with COVID-19 based on presence of:
<table>
<tr><th>New onset systemic</th><th>Endpoint Definitions</th></tr>
<tr><td>Mild</td><td>Any one of:<br>• Fever (defined by subjective or objective measure, regardless of use of anti-pyretic medications)<br>• New onset cough<br>• ≥ 2 COVID-19 respiratory/non-respiratory symptoms, AND</td></tr>
<tr><td>Moderate</td><td>≥ 1 of:<br>• Fever (≥ 37.8°C) + any 2 COVID-19 symptoms for ≥ 3 days (need not be contiguous days)<br>• High fever (≥ 38.4°C) for ≥ 3 days (need not be contiguous days)<br>• Any evidence of significant LRTI:<br>Shortness of breath (or breathlessness or difficulty breathing) with or without exertion (beyond baseline)<br>Tachypnea: 20 to 29 breaths per minute at rest<br>SpO2: < 94% on room air<br>Abnormal chest x-ray/CT consistent with pneumonia or LRTI</td></tr>
<tr><td>Severe</td><td>≥ 1 of:<br>• Tachypnea: ≥ 30 breaths per minute at rest<br>• SpO2: < 92% on room air or PAO2/FiO2 < 300<br>• High flow oxygen therapy, CPAP, or NIV (eg, CPAP/BiPAP)<br>• Mechanical ventilation or ECMO<br>• One or more major organ system failure[a] (eg, cardiac/circulatory, pulmonary, renal, hepatic to be</td></tr>
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| | | |
|---|---|---|
| Secondary objectives (Group 2) | To assess the efficacy of the candidate ChAdOx1 nCoV-19 against COVID-19 of differing severity | All secondary VE analyses will be done for the overall population and stratified by COVID-19 serological status at baseline.<br>a. VE in preventing virologically-confirmed COVID-19 clinical disease including all cases occurring onward from 21 days after a single dose.<br>b. VE in preventing virologically-confirmed COVID-19 clinical disease occurring more than 14 days after a second dose for the overall population and those that were sero-positive at baseline..<br>c. VE in preventing PCR positive COVID-19 disease cases.<br>d. VE in preventing moderate-severe virologically confirmed COVID-19 disease.<br>e. VE in preventing severe confirmed COVID-19 disease.<br>f. VE in preventing LRTI associated with virologically-confirmed COVID-19 clinical disease<br>g. VE in preventing hospitalization due to virologically confirmed COVID-19 disease<br>h. VE in preventing all-cause LRTI (overall and stratified by hospitalization or not) irrespective of test result for SARS-COV-2.<br>i. h. VE using Oxford Primary Outcome definition (PCR+ at least one symptom of fever > 37.8°C, cough, shortness of breath, anosmia, aguesia). |
| Secondary objective (Group 1 and Group 2) | To assess cellular and humoral immunogenicity of ChAdOx1 nCoV-19 | a) Enzyme-linked immunosorbent assay (ELISA) or fluorescence based micro-bead immunosorbent assay on luminex platform to quantify antibodies against SARS-CoV-2 spike protein (sero-conversion rates)<br>b) Interferon-gamma (IFN-γ) enzyme- linked immunospot (ELISpot) responses to SARS-CoV-2 spike protein<br>c) Virus neutralising antibody (NAb) assays against live and/or pseudotyped SARS-CoV-2 virus<br>d) Th1 and Th2 cytokine response profile at 3-4 days after vaccination. |
| Exploratory immunology: | To assess B cell responses to SARS-CoV-2 spike trimer and/or the receptor binding domain | a.Cellular Fc effector functionality assays to measure the ability of vaccine elicited antibodies to mediate cellular cytotoxicity, complement deposition, and phagocytosis.<br><br>b. Flow cytometric sorting of plasmablasts and memory B cells to using spike and receptor binding domain "baits" to isolate SARS-CoV-2 specific B cells, sequence their immunoglobulin genes and define their epitope specificity. |

***In adults living with HIV (HIV-infected)***

**Primary co-objectives:**

- To assess the safety of the candidate vaccine ChAdOx1 nCoV in adults living with HIV.
- To evaluate the immunogenicity of ChAdOx1 nCoV-19 after first and second doses of vaccine.

Details of objectives Group 3 (HIV-infected):

| | **Objective details** | **Endpoint measures** |
|---|---|---|
| Primary objective | To assess the safety, tolerability and reactogenicity profile of the candidate vaccine ChAdOx1 nCoV-19 in people living with HIV | a) occurrence of solicited local reactogenicity signs and symptoms for 7 days following vaccination;<br>b) occurrence of solicited systemic reactogenicity signs and symptoms for 7 days following vaccination;<br>c) occurrence of unsolicited adverse events (AEs) for 28 days following vaccination;<br>d) change from baseline for safety laboratory measures and;<br>e) occurrence of serious adverse events<br>e) occurrence of disease enhancement episodes |
| Co-primary objective | To assess cellular and humoral immunogenicity of ChAdOx1 nCoV-19 in people living with HIV after one and two doses of vaccine | a) Enzyme-linked immunosorbent assay (ELISA) or fluorescence based micro-bead immunosorbent assay on luminex platform to quantify antibodies against SARS-CoV-2 spike protein (seroconversion rates)<br>b) Interferon-gamma (IFN-γ) enzyme-linked immunospot (ELISpot) responses to SARS-CoV-2 spike protein<br>c) Virus neutralising antibody (NAb) assays against live and/or pseudotyped SARS-CoV-2 virus<br>d) Th1 and Th2 cytokine response profile at 3-4 days after vaccination. |

| | | |
|---|---|---|
| Secondary objective | To descriptively compare immune responses to ChAdOx1 nCoV-19 in people living with HIV to HIV-uninfected individuals, overall and stratified by COVID-19 sero-status at enrolment. | a) Enzyme-linked immunosorbent assay (ELISA) or fluorescence based micro-bead immunosorbent assay on luminex platform to quantify antibodies against SARS-CoV-2 spike protein (seroconversion rates)<br>b) Interferon-gamma (IFN-γ) enzyme-linked immunospot (ELISpot) responses to SARS-CoV-2 spike protein<br>c) Virus neutralising antibody (NAb) assays against live and/or pseudotyped SARS-CoV-2 virus<br>d) Th1 and Th2 cytokine response profile at 3-4 days after vaccination. |
| Exploratory immunology | To assess B cell responses to SARS-CoV-2 spike trimer and/or the receptor binding domain | a. Cellular Fc effector functionality assays to measure the ability of vaccine elicited antibodies to mediate cellular cytotoxicity, complement deposition, and phagocytosis.<br><br>b. Flow cytometric sorting of plasmablasts and memory B cells to using spike and receptor binding domain "baits" to isolate SARS-CoV-2 specific B cells, sequence their immunoglobulin genes and define their epitope specificity. |

**Formulation** Liquid

**Investigational products**

- ChAdOx1 nCoV-19, a non-replicating simian adenoviral vector expressing the spike (S) protein of SARS-CoV-2 (investigational product, IP)
- Normal saline, NaCl 0.9% as placebo

**Route of Administration** Intramuscularly (IM) into the deltoid region of the non-dominant arm

**Dose per Administration** ChAdOx1 nCoV-19 5-7.5x$10^{10}$ vp

# 2. ABBREVIATIONS

| | |
|---|---|
| **AdHu** | Human adenovirus |
| **AdHu5** | Human adenovirus serotype 5 |
| **AE** | Adverse event |
| **AID** | Autoimmune Disease |
| **CCVTM** | Centre for Clinical Vaccinology and Tropical Medicine, Oxford |
| **CBF** | Clinical Bio manufacturing Facility |
| **CEF** | Chick embryo fibroblast |
| **ChAd63** | Chimpanzee adenovirus 63 |
| **CI** | Confidence interval |
| **COP** | Code of Practice |
| **CRF** | Case Report Form or Clinical Research Facility |
| **CS or CSP** | Circumsporozoite protein |
| **CTRG** | Clinical Trials & Research Governance Office, Oxford University |
| **CTL** | Cytotoxic T Lymphocyte |
| **DSUR** | Development Safety Update Report |
| **ELISPOT** | Enzyme-linked immunospot |
| **GCP** | Good Clinical Practice |
| **GMO** | Genetically modified organism |
| **GMT** | Geometric Mean Titre |
| **GP** | General Practitioner |
| **GSK** | GlaxoSmithKline |
| **HCG** | Human Chorionic Gonadotrophin |
| **HBV** | Hepatitis B virus |
| **HEK** | Human embryonic kidney |
| **HCV** | Hepatitis C virus |
| **HIV** | Human immunodeficiency virus |
| **HLA** | Human leukocyte antigen |
| **HRA** | Health Research Authority |
| **HREC** | Human Research Ethics Committee |
| **HTLV** | Human T-Lymphotrophic Virus |
| **IB** | Investigator Brochure |
| **ICH** | *International Conference on Harmonisation* |
| ***ICMJE*** | *International Committee of Medical Journal Editors* |
| ***ICS*** | *Intracellular Cytokine Staining* |
| **IDT** | Impfstoffwerk Dessau-Tornau Biologika GmbH |
| **ID** | Intradermal |
| **IFNγ** | Interferon gamma |
| **IM** | Intramuscular |
| **IMP** | Investigational Medicinal Product |
| **IMP-D** | Investigational Medicinal Product Dossier |
| **IP** | Investigational Product |
| **IV** | Intravenous |
| **LSOC** | Local safety oversight clinician |
| **ME-TRAP** | Multiple epitopes and thrombospondin related adhesion protein |
| **MVA** | Modified vaccinia virus Ankara |

| | |
|---|---|
| **NANP** | N-acetylneuraminic acid phosphatase |
| **NHLS** | National Health Laboratory Service |
| **NICD** | National Institute for Communicable Diseases |
| **PBMC** | *Peripheral blood mononuclear cell* |
| ***Pb*** | *Plasmodium Berghei* |
| **PCR** | Polymerase chain reaction |
| **PI** | Principal Investigator |
| **pfu** | Plaque forming unit |
| **QP** | Qualified Person |
| **qPCR** | Quantitative polymerase chain reaction |
| **QS21** | *Quillaja saponaria* saponin molecule |
| **REC** | Research Ethics Committee |
| **SAE** | Serious adverse event |
| **SAHPRA** | South African Health Products Regulatory Authority |
| **SC** | Subcutaneous |
| **SmPc** | Summary of Product characteristics |
| **SOP** | Standard Operating Procedure |
| **SUSAR** | Suspected unexpected serious adverse reaction |
| **µg** | microgram |
| **vp** | viral particle |
| **VV** | viral vector |
| **WHO** | World Health Organization |