PHARMACOVIGILANCE AND CLINICAL TRIALS DIVISION

CLINICAL TRIAL APPLICATION PUBLIC ASSESSEMENT REPORT

PART 1: ADMINISTRATIVE DETAILS

Title of Study and Protocol Version: A Phase 1 Randomized Double Blinded Placebo Controlled, Dose Ranging Trial, of a Gorilla Adenovirus Vectored Networked Epitopes Vaccine (GRAdHIVNE1 Vaccine), Administered to Healthy Adults Living without HIV and Living with HIV, in Southern Africa, Version 1.0, dated 18 July 2024	**Study Ref: CT281/2024**
Date of receipt of the application: 16 October 2024	
Clinical trial Phase: Phase I	
Study Site(s): Mutala Trust, 52 Alpes Road, Vainona, Harare, Zimbabwe	
Applicant/Principal Investigator name and address: Azure Tariro Makadzange, 52 Alpes Road, Vainona, Harare, Zimbabwe	
Sponsor name and address: International AIDS Vaccine Initiative (IAVI), 125 Broad Street, 9th Floor, New York, New York 10004, USA	
Study duration: 33 months	
Date of Commencement (Expected or Actual): March 2025	
Clinical trial authorisation validity period: **7** March 2025 to 31 December 2027	

PART 2: SUMMARY OF EVALUATION
Study design: The study is a randomized, double-blind, placebo-controlled, Phase I study intended to evaluate the safety and immunogenicity of a Gorilla Adenovirus (GRAd) Vectored Networked Epitopes Vaccine (GRAdHIVNE1), administered to healthy adults living without HIV, including healthy People Living with HIV (PLWH), in Southern Africa.
Population: The study participants for the GRAdHIVNE1 vaccine trial will consist of approximately 120 healthy adults. This group will be divided into two categories: participants living without HIV (PLWoH, n=72) and participants living with HIV (PLWH, n=48) who are virally suppressed on antiretroviral therapy (ART). Participants will be aged 18 to 50 years and must meet all protocol-defined inclusion and exclusion criteria. PLWH

must have maintained viral suppression for at least six months prior to trial entry. All participants must understand the study and provide written informed consent before enrollment. Total participants worldwide is 120 participants and the expected number of participants to be recruited in Zimbabwe is 40.

Study Objectives:

Primary objectives:

1. To assess the safety and tolerability of single dose and/or homologous prime-boost schedule utilizing the GRAdHIVNE1 vaccine, administered at dosages of 5 x 10^{10} and 2 x 10^{11} viral particles in healthy people living without HIV and living with HIV.

Secondary Objectives:

1. To evaluate cellular immune responses elicited by GRAdHIVNE1 vaccine.

Exploratory Objectives:

1. To evaluate GRAd seroprevalence and induction of anti-vector neutralizing (Nab) responses in response to vaccination.
2. To assess antigen specific proliferative memory T cell responses induced by vaccination.
3. To identify immunogenic epitopes within the vaccine immunogen and define the HLA restriction.
4. To define the functional characteristics of antigen specific T cells by assessing proliferation, cytotoxicity, tetramer analysis and TCR sequences.
5. To evaluate vaccine induced innate immune responses.
6. To characterize vaccine induced de novo T-cell responses compared to pre-existing responses in PLWH (Part B).
7. To conduct analyses to further understand HIV and vaccine immunology.

Eligibility Criteria:

Inclusion Criteria

1. At least 18 years of age on the day of screening and has not reached his or her 51st birthday on the day of signing the Informed Consent Document.
2. Willing to comply with the requirements of the protocol and available for follow-up for the planned duration of the study.
3. In the opinion of the Principal Investigator or designee and based on Assessment of Informed Consent Understanding results, has understood the information provided and potential impact and/or risks linked to administration of the investigational product; written informed consent will be obtained from the participant before any study-related procedures are performed.
4. All sexually active female participants capable of becoming pregnant must commit to use an effective method of contraception from 21 days prior to receiving the IP until 4 months following the last IP administration, including:
    a. Intrauterine device, or contraceptive implant
    b. Hormonal contraception
    c. Successful vasectomy in the male partner (considered successful if a woman reports that a male partner has [1] documentation of azoospermia by microscopy (< 1 year ago), or [2] a vasectomy more than 2 years ago with no resultant pregnancy despite sexual activity post-vasectomy)
5. Women who have undergone a hysterectomy, bilateral oophorectomy, or tubal ligation, as well as those who are postmenopausal (>45 years of age with amenorrhea for at least 2 years, or any age with amenorrhea for at least 6 months and a serum

follicle stimulating hormone [FSH] level >40 IU/L) will not be required to use contraceptives.
6. Willing to forgo donations of blood, or any other tissues during the study.

Additional Inclusion criteria for PLWH (Part B only):

7. Confirmed HIV infection (HIV Ab+ or HIV RNA+) by documentation in the medical records or in-clinic HIV testing on screening visit.
8. CD4 ≥ 500 cells/µl at screening.
9. Currently on ART, and documentation of continuous combination ART (cART) for at least 12 months with suppression of plasma HIV-1 viral load < 50 copies / ml for greater than 6 months prior to trial entry, measured on at least 2 independent occasions that can include the screening viral load. cART is defined as a regimen including ≥ 2 compounds, e.g., 2 nucleoside reverse transcriptase inhibitors plus either non-nucleoside reverse transcriptase inhibitor or protease inhibitor or integrase inhibitor.
10. Viral load < 50 copies / ml at time of screening (within 28 days prior to IP administration).
11. Must commit to adhering to a suppressive ART regimen for the duration of the study

Eligibility Criteria Specific to PLWoH (Part A)

People living without HIV(PLWoH) at screening, must be deemed to be at low risk of HIV infection and willing to maintain low-risk behavior for the duration of the trial per the guidelines for determining low likelihood of acquiring HIV.

The following guidelines should be applied by the investigator to identify potential vaccine trial participants with a low likelihood of acquiring HIV. These guidelines are based on behavior within the last 12 months prior to enrollment. Some participants may not be appropriate for enrolment even if they meet these guidelines, and more stringent criteria may be applied based on the site Principal Investigator's (PI) discretion. These guidelines should be supplemented and interpreted with local epidemiological information about HIV prevalence. The site PI may review with the Medical Monitor and/or the Protocol Safety Review Team (PSRT) a participant's likelihood of acquiring HIV.

Exclusion Criteria

1. Any clinically significant acute or chronic medical condition, other than HIV infection (in Part B only), that is considered progressive or in the opinion of the investigator makes the participant unsuitable for participation in the study.
2. For the PLWH (Part B), history of AIDS-defining illness or CD4 < 200 cells/µl.
3. If female, pregnant, lactating or planning a pregnancy during the period of screening through completion of the study.
4. In the past 6 months a history of alcohol or substance use, judged by the Investigator to potentially interfere with participant study compliance.
5. Bleeding disorder that was diagnosed by a physician (e.g., Factor deficiency, coagulopathy or platelet disorder that requires special precautions). Note: A participant who states that he or she has easy bruising or bleeding but does not have a formal diagnosis and has intramuscular injections and blood draws without any adverse experience, is eligible.
6. History of a splenectomy.

7. Previous receipt of an adenovirus vectored vaccine.
8. Receipt of live attenuated vaccine or other vaccine within the previous 60 days or planned receipt within 180 days after administration of IP. Receipt of blood transfusion or blood derived products within the previous 3 months.
9. Participation in another clinical trial of an investigational product currently, within the previous 3 months or expected participation during this study.
10. Prior receipt of an investigational HIV vaccine candidate, monoclonal antibody or polyclonal immunoglobulin (note: receipt of placebo in a previous HIV vaccine or monoclonal antibody trial will not exclude a participant from participation if documentation is available and the Medical Monitor gives approval).
11. History of severe local or systemic reactogenicity to vaccines (e.g., anaphylaxis, respiratory difficulties, angioedema).
12. Psychiatric condition that compromises safety of the participant and precludes compliance with the protocol. Specifically excluded are persons with history of psychoses within the past 3 years, ongoing risk for suicide, or history of suicide attempt or gesture within the past 3 years.
13. If, in the opinion of the Principal Investigator or designee, it is not in the best interest of the participant to participate in the trial.
14. Seizure disorder: a participant who has had a seizure in the last 3 years is excluded. (Not excluded: a participant with a history of seizures who has neither required medications nor had a seizure for 3 years.)
15. Infectious disease: chronic hepatitis B infection (HbsAg positive), current hepatitis C infection (HCV Ab positive and/ or HCV RNA) or treatment for hepatitis C infection in the past year, or active syphilis (RPR confirmed by TPHA).
16. A history of malignancy within the past 5 years (prior to screening) or ongoing malignancy.
17. Active, serious infections (other than HIV infection in PLWH) requiring parenteral antibiotic, antiviral or antifungal therapy within 30 days prior to enrollment.
18. Any of the following abnormal laboratory parameters at screening:
    a. Haematology
        i. Haemoglobin <10.5 g/dL in females; haemoglobin <11.0 g/dL in males
        ii. Absolute Neutrophil Count (ANC): ≤1000/mm3
        iii. Absolute Lymphocyte Count (ALC): < 650/mm3
        iv. Platelets: < 125,000 mm3 or ≥ 550,000/mm3
    b. Chemistry
        i. Creatinine ≥1.1 x ULN
        ii. AST ≥1.25 x ULN
        iii. ALT ≥1.25 x ULN
        iv. Total bilirubin ≥1.25 x ULN
        v. Alkaline phosphatase ≥1.25 x ULN
        vi. Albumin ≤ 3.0 g/dL or ≤ 30 g/L
    c. Urinalysis
        i. Clinically significant abnormal dipstick confirmed by microscopy
        ii. Protein = 1+ or more
        iii. Blood = 1+ or more (not due to menses)

19. Any clinically relevant abnormality on history or examination including history of immunodeficiency or autoimmune disease, other than HIV among the PLWH; use of systemic corticosteroids, immunosuppressive, anticancer, or other medications considered significant by the investigator within the previous 6 months.

Vulnerable Populations
None.

Informed Consent, Decision-making & Confidentiality
Shona and English Informed Consent Forms were provided which were satisfactory.

Scientific and Technical Issues
The study design was found to be scientifically sound, the justification for the study was acceptable and follow up procedures were satisfactory. All the scientific and technical aspects were satisfactory.

Other materials, documents and study instruments (Patient recruitment materials, Questionnaires)
Recruitment materials and procedures provided were satisfactory**.**

Clinical Trials/Study Medicines

Study Medicines:

i. GRAdHIVNE1 vaccine manufactured by ReiThera S.r.l., Italy, and SGS Lab, Belgium

Comparator:
The placebo used in the study is manufactured by Adcock Ingram Critical Care (Pty) Ltd, South Africa.

The justification for the study products and the comparator was acceptable.

Summary of review of:

1. Quality
2. Safety
3. Efficacy

Quality, safety, efficacy and risk benefit analysis data was assessed and was satisfactory.

Application Review Process
The application was reviewed under the normal pathway.

Status after review:
The clinical trial application was authorised on the 7th of March 2025

PART 3: OVERALL COMMENTS AND CONCLUSION:

The Principal Investigator (PI) was required to address queries by raised by the MCAZ Pharmacovigilance and Clinical Trials Committee after the initial review of the application.

The PI managed to respond and addressed all the queries, and the PI was subsequently authorised, with the approval of the Secretary for Health and Child Care, to conduct the trial subject to the contents of the application and the following conditions:

1. Reporting of all adverse events to MCAZ;
2. Submission of all amendments to the protocol for approval by MCAZ;
3. Submission of a progress report of the clinical trial by the 31st of January annually;
4. Submission of the final report and copy of any publication of the clinical trial prior to publication of results;
5. In compliance with the current Good Clinical Practices (cGCP) and all other relevant MCAZ guidelines;
6. Submission of the completed indemnity form for conducting clinical trials to the Director-General prior to commencement of the clinical trial;
7. Expiry date of the authorisation is 31 December 2027.

Name of 1st Evaluator L. Chirinda Signature  Date: 03/09/2025

Name of 2nd Evaluator R.P. Chaitezvi Signature  Date: 04/09/2025