PART 1: Administrative Details	
Full Study Title	A Phase 2 Randomized, Double-blinded, Placebo-controlled Clinical Trial to Evaluate the Safety, Tolerability and Immunogenicity of rVSVΔGLASV-GPC Vaccine in Adults and Children Residing in West Africa
Protocol/ Document Number	IAVI C105
Date of Receipt of the Application	7th August 2023
Phase of Study	Phase II
Study Registration Details	PACTR number: PACTR202210840719552 Clinical trial certificate – No.: FDA/CT/244
Name and Address of Applicant(s)	Susan Adu-Amankwa P. O. Box LG 581, Noguchi Memorial Institute for Medical Research, University of Ghana, Legon-Accra
Name and Address of Sponsor(s)	International AIDS Vaccine Initiative (IAVI) 125 Broad Street, 9th Floor New York New York 10004 USA
Name and Address of Principal Investigator(s)	Prof. Kwadwo Koram P. O. Box LG 581, Noguchi Memorial Institute for Medical Research, University of Ghana, Legon-Accra
Study Sites	Noguchi Memorial Institute for Medical Research
Study Duration	50 Months
FAPAR Number	FDA/CT/PAR/CTA/249

PART 2: Investigational Product(s)	
Name of Investigational Product(s) including Comparator(s).	rVSVΔG-LASV-GPC Vaccine Matching placebo
Justification of Investigational Product(s) including comparators	Lassa virus (LASV) infection and Lassa fever (LF) disease are prevalent in West Africa, resulting in thousands of deaths annually, with the potential to spread globally. A safe and effective vaccine would be an effective way of preventing this disease. rVSVΔG-LASV-GPC is a candidate vaccine that has been shown to be safe and protects against LF disease in animals. The vaccine is now being

	studied in a recently completed Phase I trial and has to date been well-tolerated and immunogenic. This Phase II trial will add to data from the Phase I trial to establish a broader profile of safety and immunogenicity in adults and expand the population to include a subset of adults with HIV infection as well as older adults and healthy children, in preparation for an efficacy trial in West Africa.

PART 3: Study Summary

Study Objectives

Primary

Safety: To evaluate the safety and tolerability of rVSVΔG-LASV-GPC vaccine at 2 different dosage levels in adults, including PLWH, and in children

Secondary

Immunogenicity

• To determine LASV-GPC-specific antibody responses induced by rVSVΔG-LASV-GPC vaccine

• To determine neutralizing LASVGPC-specific antibody responses induced by rVSVΔG-LASV-GPC vaccine in a subset of participants in each group

Vaccine Distribution and Shedding

• To evaluate the magnitude and duration of the rVSVΔG-LASV-GPCvaccine viremia in plasma in a subset of participants

To evaluate the magnitude and duration of the rVSVΔG-LASV-GPC vaccine shedding in saliva and urine, and possibly semen and cervicovaginal fluid, in a subset of participants

Study Design

The study is a randomized, double-blind, placebo-controlled Phase 2 study intended to evaluate the safety, tolerability, and immunogenicity of rVSVΔG-LASV-GPC vaccine in adults and children.

There is dose escalation, with enrollment of the lower dose A cohorts followed by enrollment of the B cohorts. Cohorts 2A (lower dose for HIV-infected Adults, 18-50yrs) and 3A (Lower dose for adolescents,12-17yrs) will start enrolling at the same time as Cohort 1A (lower dose for healthy Adults, 18-70yrs). In Groups 1-4, once the A (lower dose) cohorts are enrolled, enrollment of B (higher dose) cohorts may start following favorable Protocol Safety Review Team (PSRT) review of 14-day safety data of 60% of participants in the A cohorts. Progression to the higher dose with Group 5 (Cohort 5B) will depend on review of

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cumulative safety data including Day 29 Otoacoustic Emission (OAE) testing of Cohort 5A (lower dose for children,18mos-5yrs).

In addition to dose escalation, there is age de-escalation. Prior to enrolling children 6-11 years old, the DSMB will meet to review safety data including audiometry from the first 60% of the 12-17yrs group. Likewise, prior to enrolling children 18 months to 5 years, the DSMB will meet again to review safety data from the 12-17yrs and 6-11 yrs. To ensure safety, vaccinations of the first 3 volunteers in each of the cohorts of children (6-11yrs and 18 months to 5yrs) will be separated by at least 48 hours. Also, after the first 7 participants in these cohorts have been vaccinated, enrolment will be paused for PSRT review of safety data before enrolment may continue.

Eligibility Criteria

Adults, adolescents, and children in good general health as assessed by medical history, physical examination, and laboratory tests who are ≥18 months and <71 years of age, who (themselves or as parents of minor children) are willing to comply with the requirements of the protocol and understand the information provided and potential impact and/or risks associated with the trial, are eligible to participate. People Living with HIV (PLWH) can also participate if they are on stable Highly Active Antiretroviral Therapy (HAART) therapy and meet specific criteria including viral load <50 copies/ml. Women of childbearing potential (WOCBP) must commit to use an effective method of contraception and all sexually active participants must be willing to use male or female condoms for 4 months after receipt of IP. Potential participants must be willing to forgo donation of blood or any other tissues from screening onward throughout the course of the study.

Exclusion Criteria

Potential participants will not be eligible to participate in this study if they have confirmed HIV-1 or HIV-2 infection (except for Group 2). They will also be excluded if they have any clinically relevant abnormality on history or examination or have any clinically significant acute or chronic medical condition that is considered progressive (group-specific exceptions apply). Participants must not be pregnant or lactating. Except as specifically described in the protocol, if participants have a bleeding disorder, any acute or active chronic infectious disease, history of splenectomy or other immunocompromising as well as significantly abnormal laboratory parameters, they are also excluded. They are excluded if they have recently received an investigational product (IP) in another clinical trial or have a history of severe local or systemic reactogenicity to vaccines. Participants are not eligible if they report a history of symptomatic, diagnosed Lassa fever disease (LF), or Ebola virus disease (EVD), or have received a candidate vaccine against LF. Participation will be deferred in case of other recent vaccinations. Body mass index (BMI)

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must be <35 for adults, and weight for height <2 standard deviation (SD) from median for adolescents. Weight for height/length must be >-2 SD from median for children and adolescents. They should have no psychiatric condition or substance abuse in the last 3 years that compromises their safety, nor seizure disorder in the last 3 years. Hearing must be normal for all participants or mildly reduced for adult participants aged ≥18 years and risk factors for hearing loss must be absent. Additional group-specific criteria apply.

Date of Commencement (Expected or Actual)

The study commenced on 28th June 2024

Status of Study

Study is actively enrolling participants

PART 4: Scientific Discussion

Summary of Review Comments

Quality

The quality of the Investigational product has been assessed by the FDA. The applicant submitted the following documents which were reviewed and found satisfactory to fulfil the quality requirements for the trial:

- Certificate of GMP manufacture of the Investigational product dated 1st June 2022
- Certificate of GMP manufacture of the placebo 1st June 2022

Safety

The following documents were reviewed and found satisfactory to fulfill the safety requirement of the trial:

- Investigator's Brochure Version 4.0 dated 5th January 2023

The nonclinical safety program for the rVSVΔG-LASV-GPC Vaccine included a repeat-dose toxicity study in New Zealand White rabbits with supporting data from a biodistribution study in Swiss-Webster mice. The highest rVSVΔG-LASV-GPC dose used in the toxicity and biodistribution study approximates the highest anticipated clinical dose of 2×10^7 pfu, which provides a 12-fold safety margin in rabbits over the proposed clinical dose pfu/kg basis. There was no evidence of local injection site or systemic toxicity in either of the two nonclinical studies. The nonclinical data support an acceptable tolerability and safety profile for the rVSVΔG-LASV-GPC Vaccine. The biodistribution study was conducted in Swiss-Webster mice. Animals received an intramuscular injection of 2 x 10^7 pfu of the rVSVΔG-LASV-GPC vaccine at Day 1.

PART 4: Scientific Discussion

Vaccine virus RNA sequences were detected by RT-qPCR assay in most vascularized tissues and low levels in blood and feces on Day 3. Only one sample from the entire study, an injection site of one animal, had quantifiable infectious virus (28 pfu/mg) at Day 3. The virus genome was rapidly cleared from most tissues by Day 14 and by Day 60 only the injection site, draining lymph node (inguinal/popliteal) and spleen had detectable vaccine viral RNA sequences. The Phase 1 clinical data, nonclinical pharmacology, biodistribution and toxicology data of the rVSVΔG-LASV-GPC Vaccine support the use of this vaccine in clinical studies Preclinical and clinical data from the ERVEBO® Ebola vaccine provide additional evidence for the safety of the rVSVΔG-LASV-GPC Vaccine.

Efficacy

Evaluation of the possible efficacy of the intervention was based on the information provided in the protocol and investigator's brochure.

A nonclinical immunogenicity and efficacy study conducted in non-human primates (NHP) with rVSVΔG-LASV-GPC demonstrated that one intramuscular injection with $2x10^5$ or $2x10^7$ pfus of the recombinant virus was immunogenic and protected the animals from lethal LASV challenge. Immunologic analysis showed that vaccination induced anti-GPC binding antibodies in serum and a low but detectable frequency of IFN-γ-positive GPC-specific T cells in peripheral blood. Furthermore, animals developed virus-neutralization activity in serum. Published nonclinical research studies in NHPs and guinea pigs also demonstrated previously that IM injection of a research construct of VSVΔG-LASV-GPC protected animals from lethal LASV challenge (**Investigator's Brochure Version 4.0 dated 5th January 2023**).

Overall comments

The application was deferred with queries to be addressed by the applicant after the initial review of the application. The study was authorized and given a clinical trial certificate after all queries on the submission were satisfactorily responded to.

The applicant is committed to ensuring that the study is conducted in compliance with the approved protocol, Good Clinical Practice (GCP) and applicable regulatory requirements.

All participants will consent to the protocol prior to participation in any study-related activity.

Based on the assessment of medical and ethical principles, the anticipated benefits to the participant justify the foreseeable risks and inconveniences related to the conduct study.

PART 5: Application Review Process

The application was reviewed under the routine approval pathway with a decision taken within 67 working days.

PART 6: Status after Review

The study was approved on 2nd April 2024 and is actively enrolling participants

References

- Investigator's Brochure Version 4.0 dated 5th January 2023
- Protocol Version 3.0 dated 27th March 2023
- Adult Participant Information Sheet and Consent Form version 2.0 dated 28th July 2023.
- Parental/Guardian Information Sheet and Consent Form version 2.0 dated 28th July 2023.
- Participant Information Sheet and Assent Form (12 to 14 years) version 2.0 dated 28th July 2023.
- Participant Information Sheet and Assent Form (15 to 17 years) version 2.0 dated 28th July 2023.
- Informed Consent Document for Pregnant Partner for IAVI C105 Lassa Fever Vaccine Trial version 2.0 dated 28th July 2023
- Clinical Assessment of Clinical Trial Application version 01 dated 2nd September 2019.
- Quality Assessment of Clinical Trial Application version 01 dated 2nd September 2019.
- ICH E6(R2) guideline for good clinical practice dated 9 November 2016.
- ICH E2A guideline for clinical safety data management: definitions and standards for expedited reporting dated 27 October 1994.
- ICH E8 general considerations for clinical trials dated 17 July 1997
- ICH E9 statistical principles for clinical trials dated 05 February 1998
- ICH E10 choice of control and related issues in clinical trials dated 20 July 2000
- ICH E17 general principles for planning and design of multi-regional clinical trials