SUMMARY EVALUATION REPORT TEMPLATE

Study Title: " A Phase 2, Randomized, Double-blind, Placebo-Controlled Trial to Evaluate Safety, Tolerability, and Immune Responses of an Investigational Monovalent Chimpanzee Adenoviral-Vectored Sudan Ebolavirus Vaccine in Healthy Adults. Short Title: Sabin 003, **"**
NDA CTA Number: CTA 0265
Protocol No. Amendment 2.0
Version No. 2.0 **Date:** 15 May 2024
National Principal Investigator (NPI): Dr. Betty Mwesigwa
Institution /Trial Site: Makerere University Walter Reed Project
Sponsor: Sabin Vaccine Institute
REC of Record: Makerere University, College of Health Sciences- School of Public Health REC **REC Reference number: --**
UNCST Refence Number: HS3628ES
NDA date of Approval: 11th April 2024

Study background and Rationale

Currently there are no approved vaccines or therapeutics to treat individuals infected with SUDV. Vaccines with durable protective immunity would be desirable for populations in areas of the world where outbreaks occur sporadically. The primary goal of the cAd3-EBO S vaccine development program is to create a safe and efficacious vaccine that can induce rapid immunity followed by durable protection against SUVD. Previous studies have evaluated the safety and immunogenicity of the cAd3-EBO S vaccine in a small group of healthy adults up to 50 years of age in the United States. This Phase 2 study will evaluate the safety, tolerability, and immunogenicity of the cAd3-EBO S vaccine in healthy adults up to 70 years of age in an African population.

General objective / Study aims

To evaluate the safety and tolerability of cAd3-EBO S vaccine
Primary endpoint.
Count and percentage of vaccinated participants who develop:

- SAEs,
- Solicited AEs,
- Unsolicited AEs,
- AESI,
- MAAE,

- AE at each intensity level.

Estimand 1a (Primary): Count and percentage of vaccinated participants who would develop SAEs, solicited AEs, unsolicited AEs, AESI, MAAE, and AE at each intensity level will be evaluated with each treatment group. A treatment policy strategy is used for assessing safety irrespective of a current (or prior) infection at time of the vaccination. Infections and death (if they meet the AE and time window criteria) are included in the endpoint (composite strategy)

Primary Objectives and Outcome Measures

To evaluate the safety and tolerability of cAd3-EBO S vaccine

Primary endpoint.

Count and percentage of vaccinated participants who develop:

- SAEs,
- Solicited AEs,
- Unsolicited AEs,
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Secondary Objectives and Outcome Measures

- To evaluate the antibody response (IgG) to cAd3-EBO S vaccine at Day 29 post-vaccination.

Secondary endpoints

- GMC of anti-Sudan Ebolavirus
- GP binding IgG antibodies at Day 29 post-vaccination.

Estimand 2a: GMC of the vaccine group will be compared to placebo at Day 29 post-vaccination. The hypothetical strategy is used to estimate antibody levels without subsequent SUDV infection or influence from immune-modifying drugs or non-study vaccines. The principal stratum strategy excludes those with active or prior SUDV infection at the time of the vaccination.

- To determine the antibody (IgG) response to cAd3- EBO S vaccine across additional time points post vaccination.

Endpoints

GMCs of anti-Sudan Ebolavirus-GP binding IgG antibodies at Day 1, Day 8, Day 15, Day 29, Day 85, Day 169, and Day 366. • GMI of anti-Sudan Ebolavirus-GP binding IgG antibodies at Day 29 post-vaccination and optional selected timepoints (Day 8, Day 15, Day 85, Day 169, and Day 366).

Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled study evaluating the safety and tolerability and immune response of an investigational monovalent cAd3-EBO S vaccine for prevention of disease caused by SUDV and for SUDV outbreak control. At Screening, adult participants will be screened for eligibility up to 28 days before enrollment. Participants will be screened in order to provide approximately 125 participants enrolled and vaccinated in the study. Enrollment will be staggered, starting with healthy adults 18 to 50 years of age (inclusive). Upon enrollment of a minimum of 25 younger adult participants (sentinel), the safety data up to 7 days postvaccination of these 25 sentinel participants will be reviewed by the independent Data Safety Monitoring Board (DSMB). Enrollment will continue in this age group (expansion) without pause. Progression to enrollment of the older adults (>50 to 70 years of age) will be dependent on the safety review by the DSMB.

Study Population

Healthy Participants 18 years and above

Eligibility Criteria

Inclusion Criteria:

Each participant must meet all of the following criteria to be enrolled in this study:
1. Able and willing to complete and provide written informed consent prior to any study procedure, completing an Assessment of Understanding (AoU) prior to enrollment by answering 9 out of 10 questions correctly at least once in 3 attempts, and including optional consent for retention of blood samples for potential future testing and assay development.
Note: Participants can be enrolled even if they do not provide optional consent for retention of blood samples for potential future testing and assay development.
2. Able to read and write the language used in diary card.
3. Male or non-pregnant female 18 to 70 years of age (inclusive) at time of informed consent.

4. Is capable of understanding and agrees to comply with planned study procedures and to be available for all clinic follow-up for all planned study visits.
5. Able to provide proof of identity to the satisfaction of the study clinician completing the enrollment process.
6. Has a means to be contacted and to contact the investigator during the study.
7. Agree not to receive any vaccine within 28 days from study vaccination (prior and after), with the exception of an emergency use authorization or authorized non-adenoviral vectored COVID-19 vaccine, which may be given within 14 days of study vaccination.
8. Agree not to donate bone marrow, blood, or blood products until 3 months after the study vaccination.
9. In good general health without clinically significant medical conditions, based on medical history, physical examination, vital signs, and clinical laboratory results as deemed acceptable by the principal investigator.
10. Clinical laboratory results within 28 days prior to vaccination within the site's laboratory reference ranges (or deemed not clinically significant by the principal investigator) for the following parameters: hematology (CBC including hemoglobin, WBC, RBC, total lymphocyte count); coagulation tests (prothrombin time in terms of INR, d-dimer, INR, fibrinogen); chemistry (C-reactive protein, ALT, AST, and serum creatinine). A laboratory result that is outside the reference range and is deemed not clinically significant by the principal investigator will not exclude the participant.
11. Has a BMI >17 and ≤37 at screening.

Female participant-specific criteria:

12. Negative pregnancy serum test at screening, and negative urine pregnancy test before vaccination, if of reproductive potential.
13. Agrees to use an effective means of birth control from at least 21 days prior to enrollment through 24 weeks after study vaccination if assessed to be woman of childbearing potential UNLESS they fulfill one of the following criteria: • At least 1 year postmenopausal. • Surgically sterile.

Male participants must agree:

14. Not to father a child or donate sperm through study end.
15. To use a barrier (condom) means of birth control from vaccination through study end, if assessed to be of reproductive potential.

Exclusion criteria:

Participants meeting any of the following criteria will be excluded from the study:
1. Pregnant or lactating female or plans to become pregnant or breastfeed starting from study vaccination through to study end.
2. Has any medical disease or condition that, in the opinion of the investigator, precludes study participation. This includes any acute, subacute, intermittent, or chronic medical disease or condition that:

• would place the participant at an unacceptable risk of injury,
• render the participant unable to comply with the requirements of the protocol,
• or may interfere with the evaluation of responses or the participant's successful completion of the trial (chronic conditions that are well-controlled and medically stable, i.e., no change in treatment for medical reasons occurred in the last 6 months and are allowed at the discretion of the principal investigator, e.g., hypertension, asthma, thyroid disease).
The medical disease or condition also includes any confirmed or suspected immunosuppressive or immunodeficient conditions resulting from disease (e.g., malignancy, HIV infection) or immunosuppressive/cytotoxic therapies (e.g., medications
used during cancer chemotherapy, organ transplantation or to treat autoimmune disorders).
3. Serology screen positive for infectious diseases (hepatitis B, hepatitis C, HIV 1 and 2, syphilis).
4. Known history of prior exposure to SUDV or prior diagnosis of SUVD, determined from the participant's reported medical history.
5. Current diagnosis of COVID-19 by Reverse Transcription Polymerase Chain Reaction (RT-PCR) or antigenic testing or current signs and symptoms of COVID-19. Participants may be enrolled 14 days post resolution of all signs and symptoms of COVID-19 or of testing positive for COVID-19 in asymptomatic participants.
6. History of or active status of any of the following clinically significant conditions:
• Serious adverse reactions to vaccines such as anaphylaxis, urticaria (hives), respiratory difficulty, angioedema, or abdominal pain.
• Allergic reaction to excipients in the study vaccine including gentamycin, neomycin or streptomycin or any other aminoglycoside.
• Diabetes mellitus type 1 or type 2.
• Active tuberculosis.
• Hereditary angioedema, acquired angioedema, or idiopathic forms of angioedema.
• Idiopathic urticaria within the last year.
• Bleeding disorder diagnosed by a doctor (e.g., factor deficiency, coagulopathy, or platelet disorder requiring special precautions), use of anticoagulant medications such as warfarin, apixaban, or dabigatran, or significant bruising or bleeding difficulties with IM injections or blood draws.
• Major thrombotic event or heparin-induced thrombocytopenia or Vaccine-Induced Thrombotic Thrombocytopenia (VITT).
• Malignancy of any organ system, treated or untreated, within the past 5 years from screening (if diagnosed malignancy is 5 or more years prior to enrollment and cured with no ongoing treatment it will NOT be considered an exclusion).
• Seizure in the past 3 years or treatment for seizure disorder in the past 3 years.
• Asplenia or functional asplenia.
• Autoimmune disease/autoinflammatory condition.

Any medical, psychiatric, social condition, occupational reason, or other responsibility that, in the judgment of the investigator, is a contraindication to protocol participation or impairs a participant's ability to give informed consent.
7. Has a clinically significant acute illness (this does not include minor illnesses) or temperature ≥38.0°Celsius (≥100.4° Fahrenheit) within 24 hours of the planned dose of study vaccine. Re-evaluation of eligibility may be performed at resolution of all signs and symptoms, and randomization at a later date is permitted at the discretion of the investigator and after consultation with the sponsor (as appropriate).
8. Receipt of any of the following substances:
• COVID-19 vaccine that has not received emergency use authorization or approval per local regulatory agency.
• Prior receipt of Ebola or Marburg vaccine.
• Prior receipt of any adenoviral-vectored vaccine, adenovirus-based or adeno-associated virus (AAV)-based gene therapies or treatments, including adenoviral COVID-19 vaccines or boosters.
• Participant received an investigational drug (including investigational drugs for prophylaxis of COVID-19) within 28 days of dosing or within washout period (5 half-lives) of such drug or has used an invasive investigational medical device within 28 days of dosing.
• Received investigational Ig or monoclonal antibodies within 3 months.
• Received convalescent serum for COVID-19 treatment within 3 months.
• Received an investigational vaccine within 3 months before the planned administration of the first dose of study vaccine.
• Is currently enrolled or plans to participate in another investigational or interventional study during this study (observational/registry studies are allowed).
9. Use of immunomodulators or systemic glucocorticoids in daily doses of glucocorticoid equivalence >20 mg of prednisolone in the last 90 days, and for periods exceeding 10 days. Non-Steroidal Anti-Inflammatory Drugs (NSAIDS) are permitted.
10. Receipt of blood products within 3 months prior to enrollment.
11. Current anti-tuberculosis prophylaxis or therapy.
12. Abnormality or permanent body art (such as tattoo) in deltoid region that would interfere with ability to observe or assess injection site reactions.

Study Duration

24 months

Investigational Medicinal Product

cAd3-EBO Sudan Vaccine

Study Arms

Participants will be randomly assigned at Day 1 (Visit 1) to receive cAd3-EBO S vaccine or placebo using a 4:1 allocation ratio.

Sample size

125 participants worldwide and 80 participants in Uganda.

Evaluator's Risk/Benefit Assessment:

The current information on the investigational product is sufficient to justify the proposed clinical trial and ensure compliance with Good Clinical Practice. The potential benefits of conducting the trial are considered to outweigh the risks involved, provided that the study is carried out in accordance with the approved protocol, applicable local regulatory standards, ethical standards derived from the Declaration of Helsinki and the principles of Good Clinical Practice.