A Phase 1, Randomized, Recipient- and Observer-Blinded, Dose-Escalation Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of Two Doses of Rabies-Vectored Monovalent Lassa Fever Vaccine (LASSARAB) Administered with 3D-(6-Acyl) PHAD-SE (aPHAD-SE) Adjuvant in Healthy Adults

DMID Protocol Number: 23-0015

IND Number: 30607

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Version Number: 6.0
13 June 2025

STATEMENT OF COMPLIANCE

Each institution engaged in this research will hold a current Federalwide Assurance (FWA) issued by the Office of Human Research Protection (OHRP) for federally funded research. The IRB/IEC must be registered with OHRP as applicable to the research.

The study will be carried out in accordance with the following as applicable:

- United States Code of Federal Regulations (CFR) 45 CFR Part 46: Protection of Human Subjects
- Food and Drug Administration (FDA) Regulations: 21 CFR Part 50 (Protection of Human Subjects), 21 CFR Part 54 (Financial Disclosure by Clinical Investigators), 21 CFR Part 56 (Institutional Review Boards), 21 CFR Part 11, and 21 CFR Part 312 (Investigational New Drug Application), and/or 21 CFR 812 (Investigational Device Exemptions)
- The International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E6(R2) Good Clinical Practice, and the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
- The policies and procedures of National Institutes of Health (NIH) Office of Extramural Research and DMID
- The National Institute of Allergy and Infectious Diseases (NIAID) Terms of Award
- Any additional Federal, State, and Local Regulations and Guidance

The signature below provides the necessary assurance that this study will be conducted according to all stipulations of the protocol including statements regarding confidentiality, and according to local legal and regulatory requirements, US federal regulations, and ICH E6(R2) Good Clinical Practice (GCP) guidelines.

Site Investigator Signature:

Signed: _____ Date: _____

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1. PROTOCOL SUMMARY

1.1 Synopsis

Rationale for Proposed Clinical Study

Lassa fever is a zoonotic infection endemic in West Africa and is spread by the Lassa virus, an arenavirus causing hemorrhagic fever. Up to 300,000 Lassa fever infections occur annually and while disease is often mild, in a subset of individuals disease is characterized by severe anemia, bleeding, encephalopathy, respiratory failure, shock, and high mortality.[1] In some regions of West Africa, up to 15% of hospital admissions are secondary to Lassa fever, and an estimated 5,000 deaths occur annually.[2] During epidemics of disease, case-fatality rates may reach as high as 50% in hospitalized patients.[1] Approximately one-third of infected individuals will develop hearing loss regardless of disease severity, and in a proportion of patients, permanent deafness occurs.[1]

Prevention of illness through vaccination is a critical goal in reducing the burden of disease from Lassa fever. There are currently no vaccines or therapeutics demonstrated to be efficacious in the prevention or treatment of Lassa fever.[3]

This study proposes the evaluation of a novel, first-in-human Lassa fever vaccine based on the complete Lassa glycoprotein complex (GPC) antigen. The antigen will be presented on a genetically modified and attenuated rabies vector expressing both the rabies glycoprotein (GP) antigen and the Lassa GPC. The inactivated chimeric virus is delivered with a toll-like receptor 4 (TLR-4)-activating oil-in-water emulsion adjuvant. Studies using this vaccine administered as a prime-boost series in mice and non-human primates, and then challenged with Lassa virus demonstrated significant protection against Lassa fever.[4-6] Given that the vaccine backbone is an attenuated and inactivated rabies virus expressing rabies GP, this vaccine will also be evaluated for immunogenicity against rabies virus.

Study Design

This is a phase 1, randomized, controlled, recipient- and observer-blinded, dose-escalation clinical trial to evaluate the safety, tolerability, and immunogenicity of LASSARAB+aPHAD-SE vaccine candidate compared to a licensed rabies virus vaccine control (HDCV), each administered as intramuscular (IM) doses on Days 1 and 29 in adult participants aged 18 through 50 years. The trial will enroll up to 55 healthy participants. The study treatment groups are summarized in Table 1. If all 55 participants are enrolled and vaccinated, the randomization will be 3:3:3:2 of LASSARAB 700rU dose, LASSARAB 1400rU dose, LASSARAB 2800rU dose (2 injections of 1400rU), and HDCV comparator.

Table 1. Study Treatment Arms

Treatment Group	Number of Participants	Product	Antigen Dose	Adjuvant Dose	Frequency of Administration
A	15	LASSARAB+ aPHAD-SE	700rU	5µg	D1, D29

B	15	LASSARAB+ aPHAD-SE	1400rU	5µg	D1, D29
C	15	LASSARAB+ aPHAD-SE	1400rU per injection (2 injections)	5µg per injection (2 injections)	D1, D29
D	10	HDCV	≥2.5 IU rabies antigen	N/A	D1, D29

Note: Treatment Group C will receive two simultaneous injections of the LASSARAB 1400rU dose vaccine. Therefore, each participant in treatment Group C will receive a total 2800rU LASSARAB and 10µg aPHAD-SE. Some Group D participants will receive an injection of normal saline placebo simultaneous to HDCV to maintain blinding of Group C. See Table 2 for details.

Participants will be recruited from the greater Washington/Baltimore Metropolitan Area. The trial will be conducted by a single center, the Center for Vaccine Development and Global Health (CVD) at the University of Maryland, Baltimore (UMB). Participants will be screened to determine eligibility for enrollment. Screening will include evaluations for general health, factors that may increase the risk to participants in the trial, and factors that could confound interpretation or execution of the study. Eligible participants will be enrolled and randomized to treatment groups using block randomization for each cohort generated by the unblinded study statistician. Participants will then be vaccinated in a dose escalating process as shown in Table 2 and in Section 1.3. The investigators, study staff (excluding vaccine administrators), and study participants will be blinded to the treatment each participant receives. Adverse events (AEs) will be assessed by blinded study clinicians for severity using relevant DMID toxicity tables and for the relationship of the event to the study product treatment.

For this trial, a conservative dose escalation design is used in which each treatment group of 15 vaccine recipients is split into two subgroups. The first subgroup, termed the "sentinel subgroup," includes 4 vaccine recipients. The second subgroup, termed the "expanded subgroup," includes the remaining 11 vaccine recipients. In each of the three initial treatment groups (Group A, Group B, and Group C), enrollment is paused for 7 days after vaccination of the sentinel subgroup for safety review.

Study participants will be divided into four vaccination cohorts.

- In Cohort 1, there will be 4 LASSARAB 700rU dose recipients (Group A sentinel subgroup) and 1 HDCV control recipient. If no Sentinel Subgroup Halting Criteria are met after 7 days of safety monitoring, an Independent Safety Monitor (ISM) will recommend proceeding to vaccinate Cohort 2.
- In Cohort 2, there will be 4 LASSARAB 1400rU dose recipients (Group B sentinel subgroup), 3 HDCV control recipients, and 11 LASSARAB 700rU dose recipients (Group A expanded subgroup). If no Sentinel Subgroup Halting Criteria are met after 7 days of safety monitoring, the ISM will recommend proceeding to vaccinate Cohort 3.
- In Cohort 3, there will be 4 recipients of two simultaneous injections of LASSARAB 1400rU dose product (Group C sentinel subgroup), 3 HDCV control recipients, and 11 single-injection LASSARAB 1400rU dose recipients (Group B expanded subgroup). If no Sentinel Subgroup Halting Criteria are met after 7 days of safety monitoring, the ISM

will recommend proceeding to vaccinate Cohort 4.

- In Cohort 4, there will be 3 HDCV control recipients, and 11 recipients of two simultaneous injections of LASSARAB 1400rU dose product (Group C expanded subgroup).

Table 2. Dose Escalation Schedule

Cohort	Group	Number of Participants	Group Type	Injection #1 Treatment	Injection #2 Treatment
1	A	4	Sentinel	LASSARAB 700rU Dose	N/A
	D	1	Control	HDCV control	N/A
	Total	5			
2	A	11	Expanded	LASSARAB 700rU Dose	N/A
	B	4	Sentinel	LASSARAB 1400rU Dose	N/A
	D	3	Control	HDCV control	N/A
	Total	18			
3	B	11	Expanded	LASSARAB 1400rU Dose	N/A
	D	2	Control	HDCV control	N/A
	C	4	Sentinel	LASSARAB 1400rU Dose	LASSARAB 1400rU Dose
	D	1	Control	HDCV control	Normal saline placebo
	Total	18			
4	C	11	Expanded	LASSARAB 1400rU Dose	LASSARAB 1400rU Dose
	D	3	Control	HDCV control	Normal saline placebo
	Total	14			

Note: Treatment Group C will receive two vaccine injections administered in bilateral arms simultaneously. Therefore, each participant in treatment Group C will receive a total 2800rU LASSARAB and 10 µg aPHAD-SE. To maintain blinding of participants in Cohorts 3 and 4, one dose of normal saline placebo will be administered in the contralateral arm to one participant receiving HDCV control in Cohort 3 and to all three participants receiving HDCV control in Cohort 4.

There will be no further planned ISM safety reviews for dose escalation after Cohort 4, although study investigators will continue to monitor for safety and apply relevant Individual Halting Criteria and General Study Halting Criteria and safety procedures when applicable. To maintain blinding of participants in Cohort 3 and 4, one dose of normal saline placebo will be administered simultaneously in the contralateral arm in some participants receiving HDCV control (See Table 2 for details).

Participants will be monitored for one year following the second study vaccination (through Day 394). A paper Diary Card will be used to collect solicited and unsolicited AE information covering the 7-day period following each study vaccination. Safety laboratory analyses will be performed on Day 8 and Day 36 (7 days following each study treatment), as well as on Day 61. Blood samples will be obtained for immunological assays at Days 1, 8, 29, 36, 61, 121 and 394. Left-over and additional blood specimens will also be retained and collected for future use.

Unsolicited adverse events will be collected through Day 61 (32 days after the last study treatment). Only a subset of AEs will be collected beyond Day 61; these are serious adverse

events (SAEs), medically-attended adverse events (MAAEs), new-onset chronic medical conditions (NOCMCs), potential immune-mediated medical conditions (PIMMCs), and an adverse event of special interest (AESI) – new onset sensorineural hearing loss (SNHL). SNHL will be assessed by audiometry at screening, after the first vaccine dose at Day 22, after the second vaccine dose at Day 61, upon completion of the study at Day 394, and at any time if the participant reports change in hearing or at the discretion of the Principal Investigator (PI). SAEs, MAAEs, NOCMCs, PIMMCs, and the AESI will be collected through Day 394 (the end of the study, approximately one year after the second study vaccination). See Section 7.1.5 for SNHL definitions and evaluation procedures and see Appendix 7 for the list of specific PIMMCs to be reported.

An interim analysis of the Primary and Secondary Endpoints will be performed with all data and samples collected through Day 61. These analyses will be reported in an interim clinical study report (CSR). To maintain blinding of principal investigator, sponsor, and blinded study staff, results will be presented in summary tables by Treatment Arm. Data and studies from blood samples collected after Day 61 will be reported in separate CSRs. Assessed exploratory endpoints will also be included in the final CSR.

Study Objectives and Endpoints

Primary Objective	Primary Endpoint
To assess the safety and reactogenicity of escalating doses of the LASSARAB+ aPHAD-SE vaccine candidate administered at Day 1 and Day 29	• Number and percentage of participants experiencing solicited local and systemic reactogenicity AEs through 7 days after each study vaccination (From Day 1 through Day 8 for the first vaccination and from Day 29 through Day 36 for the second vaccination) • Number and percentage of participants experiencing any unsolicited AEs from Day 1 through Day 61 • Number and percentage of participants experiencing any of the following from Day 1 through Day 394: • Serious Adverse Events (SAEs), • Medically-Attended Adverse Events (MAAEs), • New-Onset Chronic Medical Conditions (NOCMCs), • Potential Immune-Mediated Medical Conditions (PIMMCs), • Adverse Event of Special Interest (AESI)—new onset sensorineural hearing loss (SNHL) • Number and percentage of participants experiencing clinical laboratory AEs through Day 61

Secondary Objective	Secondary Endpoint

To evaluate the Lassa antibody response at escalating doses of the LASSARAB+aPHAD-SE vaccine candidate administered at Day 1 and Day 29	• Geometric mean IgG titers (GMT) to LASSA GPC by enzyme linked immunosorbent assay (ELISA) at Day 1, 8, 29, 36, and 61 per treatment group • Percentage of participants seroconverting for Lassa GPC IgG antibodies at Day 8, 29, 36, and 61 per treatment group (where seroconversion is defined as > 4 fold rise in antibody titer at any time point as compared to baseline.)
To evaluate the rabies antibody responses to LASSARAB+aPHAD-SE vaccine candidate administered at Day 1 and Day 29	• Percentage of participants with rabies antibody titers by the RFFIT test (Rapid Fluorescent Foci Inhibition Test) at Day 8, 29, 36, and 61 per treatment group • Geometric mean IgG titers (GMT) to rabies GP by ELISA at Day 8, 29, 36, and 61 per treatment group • Percentage of participants seroconverting for rabies antibodies at Day 8, 29, 36, and 61 per treatment group (where seroconversion is defined as > 4 fold rise in antibody titer at any time point as compared to baseline.)

Exploratory Objective	**Exploratory Endpoint**
To evaluate the durability of Lassa antibody responses to LASSARAB+aPHAD-SE vaccine candidate	• Geometric mean IgG titers (GMT) to LASSA GPC by ELISA at Day 121, and 394 per treatment group • Percentage of participants seroconverting for Lassa GCP antibodies at Day 121, and 394 per treatment group (where seroconversion is defined as > 4 fold rise in antibody titer at any time point as compared to baseline).
To evaluate the rabies antibody responses to LASSARAB+aPHAD-SE vaccine candidate	• Percentage of participants with rabies antibody titers by the RFFIT test (Rapid Fluorescent Foci Inhibition Test) at Day 121 and 394 per treatment group • Geometric mean IgG titers (GMT) to rabies GP by ELISA at Day 121 and 394 per treatment group • Percentage of participants seroconverting for rabies antibodies at Day 121 and 394 (where seroconversion is defined > 4 fold rise in antibody titer at any time point as compared to baseline).

Inclusion criteria: In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provides written informed consent prior to the initiation of any trial procedures.
2. Able to understand and agrees to comply with all planned trial procedures and be available for all study visits.
3. Age ≥ 18 and ≤50 years at time of enrollment.
4. In good general health[1] and without clinically significant medical, psychiatric, chronic or intermittent health conditions including those listed in Exclusion Criteria (Section 5.2).

[1] *As evidenced by medical history, medication use, and physical examination to*

evaluate ongoing chronic medical or psychiatric diagnoses or conditions, defined as those that have been present for at least 60 days, which would not affect the assessment of the safety of participants or the immunogenicity of study vaccinations. These medical diagnoses or conditions should be stable for the last 60 days (no hospitalizations, emergency room [ER] or urgent care for condition [excluding musculoskeletal conditions]), or invasive medical procedure and no adverse symptoms that need medical intervention such as medication change/supplemental oxygen). This includes no change in chronic prescription medication or dose in the 60 days prior to enrollment. Any prescription change that is due to change of health care provider, insurance company, etc., or that is done for financial reasons, as long as in the same class of medication, will not be considered a deviation of this inclusion criterion. Participants may be on chronic or as needed (prn) medications if, in the opinion of the PI or appropriate sub-investigator, they pose no additional risk to participant safety or assessment of reactogenicity and immunogenicity and do not indicate a worsening or treatment of continued symptoms of medical diagnosis or condition. Note: Low dose topical corticosteroids as outlined in the Participant Exclusion Criteria (Section 5.2) as well as herbals, vitamins, and supplements are permitted.

5. Participants of childbearing potential[2] must have a negative serum human chronic gonadotropin (HCG) pregnancy test at screening and a negative urine HCG pregnancy test within 24 hours prior to the study vaccination.

   [2]Not of childbearing potential - post-menopausal females (defined as having a history of amenorrhea for at least one year) or a documented status as being surgically sterile (hysterectomy, bilateral oophorectomy, salpingectomy, or Essure® placement with history of documented radiological confirmation test at least 60 days after the procedure).

6. Participants of childbearing potential[3] in a heterosexual relationship agree to use of highly effective contraception[4] beginning at the time of the screening visit through Day 61 (32 days after the last study treatment).

   [3]Not of reproductive potential means post-menopausal participants born female (defined as having a history of amenorrhea for at least one year) or a documented status as being surgically sterile (hysterectomy, bilateral oophorectomy, tubal ligation/salpingectomy, or Essure® placement with history of documented radiological confirmation test at least 90 days after the procedure). These criteria are applicable to female participants in a heterosexual relationship AND of reproductive potential. These criteria do not apply to participants in a same sex relationship.

   [4]Acceptable forms of primary contraception include true abstinence (100% of time no insertional sexual intercourse), monogamous relationship with a vasectomized partner who has been vasectomized for 180 days or more prior to the participant

receiving the vaccination, intrauterine devices, birth control pills, condoms with spermicide, and injectable/implantable/insertable/transdermal hormonal birth control products. Must use at least one acceptable primary form of contraception for at least 30 days prior to enrollment and through the end of the study.

7. Vital signs[5] and Body Mass Index (BMI) are in the following ranges at screening:
   - Oral temperature is less than 100.4°F (38.0°C).
   - Pulse is 47 to 100 beats per minute, inclusive.
   - Systolic blood pressure (SBP) is 85 to 140 mmHg, inclusive.
   - Diastolic blood pressure (DBP) is 55 to 90 mmHg, inclusive.
   - BMI of 18 kilograms/square meter (kg/m^2) (inclusive) to <35 kg/m^2

   [5]Vital signs meeting Grade 1 severity criteria (Appendix 5) and not clinically significant may be eligible as determined by the investigator.
8. Has a negative test result for hepatitis B virus (HBV) surface antigen, hepatitis C virus (HCV) antibody[6], and human immunodeficiency virus (HIV) types 1 or 2 antibodies at screening.

   [6]Persons testing positive for hepatitis C virus antibody with a history of treatment and a negative HCV viral load may be acceptable in the opinion of the PI or designated clinician licensed to make medical diagnoses and listed on Form FDA 1572.
9. Has a negative rabies neutralizing antibody test at screening (< 0.5 IU/mL in RFFIT assay)
10. Screening hematology tests (white blood cells, hemoglobin, and platelets) and screening chemistry tests (alanine transaminase, creatine, and total bilirubin) are within acceptable parameters[7]

    [7]Screening laboratory values within institutional laboratory normal limits or Grade 1 abnormalities if deemed not clinically significant by the investigator are eligible.
11. Must agree to the collection and storage of residual biological specimens and additional clinical specimens for secondary research use (Section 10.1.4)
12. Agreement to adhere to Lifestyle Considerations (Section 5.4 during the study.[8]

    [8]Deviations of Lifestyle Considerations will be reported as protocol deviations but not as eligibility deviations.

Exclusion criteria: An individual who meets any of the following criteria will be excluded from participation in this trial:

1. A history of anaphylaxis, serum sickness, meningitis; neuroparalytic events such as encephalitis, transient paralysis; Guillain-Barré Syndrome; myelitis; retrobulbar neuritis; history of prior or current hearing loss as assessed by quantitative audiometry (Section 7.1.5); or multiple sclerosis
2. Current use of any medications that may be associated with impaired immune

responsiveness[1]

[1]*Including, but not limited to, corticosteroids exceeding 10 mg/day of prednisone equivalent, allergy injections, immunoglobulin, interferon, immunomodulators, cytotoxic drugs, or systemic corticosteroids or other similar or toxic drugs during the preceding 4-month period prior to screening. Low dose topical and intranasal steroid preparations used for a discrete period of time are permitted.*

3. Allergy treatment with antigen injections within 60 days before first vaccination or that are planned through the end of the study.
4. Receipt of immunoglobulins and/or any blood products within the 60 days before first vaccination or that are planned through the end of the study.
5. Current pregnancy or lactation.
6. Known allergic reactions to 1) any rabies vaccine; 2) any components of HDCV (human albumin, neomycin sulfate, phenol red, beta-propiolactone); 3) any components of LASSARAB +aPHAD-SE (LASSARAB, Tris-HCI, L-Arginine, (3D -(6-Acyl) PHAD, Squalene Redistilled, DMPC, Vitamin E Dry Powder).
7. History of severe local or systemic reactions to any vaccination or a history of severe allergic reactions to drug or vaccine products.
8. Has a significant acute illness (with or without fever), as determined by the site PI or appropriate sub-investigator, within 72 hours prior to enrollment[2]

   [2]*If the participant meets all other eligibility criteria, they may be enrolled and dosed once they meet this eligibility criterion. If the illness resolves within the 60-day screening window, they do not need to be rescreened, otherwise they will need to be rescreened.*
9. Receipt of a rabies vaccine or an antibody therapeutic product for treating rabies or a Lassa fever vaccine any time before the first planned study vaccination.
10. Receipt of another experimental agent or intervention within 60 days before first vaccination or plans to do so before the end of the study.
11. Received or plans to receive any other vaccine in the 2 weeks prior to the first vaccination through Day 61 (32 days after the last study treatment).
12. Received or plans to receive any live vaccine in the 4 weeks prior to first vaccination through Day 61 (32 days after the last study treatment).
13. Self-reported or known history of alcoholism within the last 2 years.
14. Any condition that, in the judgment of the investigator, precludes participation because it could affect participant safety or endpoint assessment.
15. Has tattoos, scars, or other marks which would, in the opinion of the investigator, interfere with assessment of the vaccination site.

Study Phase: Phase 1

Study Population: Up to 55 generally healthy persons aged 18 through 50 years

Sites: One site, Center for Vaccine Development and Global Health (CVD) University of Maryland School of Medicine

Study Intervention: The investigational vaccine (LASSARAB) is a Lassa virus (LASV) glycoprotein complex (GPC) antigen presented on a chemically inactivated and modified rabies virus vector (RABV). This study will evaluate the safety, reactogenicity, and immunogenicity conferred by two doses of the vaccine LASSARAB (inactivated rabies virus vector, RABV, expressing LASV GPC), adjuvanted with a synthetic Toll-like receptor 4 agonist, 3D-(6-acyl) PHAD (Monophosphoryl Hexa-acyl Lipid A, 3-Deacyl) in stable oil-in-water emulsion (SE), together as aPHAD-SE. The LASSARAB vaccine antigens are presented on a beta-propiolactone chemically inactivated and attenuated platform and administered in combination with the aPHAD-SE adjuvant formulation in a two-dose series. Pre-clinical studies have shown that LASSARAB with a similar adjuvant given to non-human primates, administered on Days 1 and 29, led to protection upon subsequent Lassa virus challenge, while non-human primates administered a different RABV-based vaccine succumbed to illness upon challenge (internal data).

In a dose escalation procedure, three doses of LASSARAB+ aPHAD-SE will be evaluated (LASSARAB 700rU dose, LASSARAB 1400rU dose, and LASSARAB 2800rU dose). All vaccine components are liquid and will be mixed with a fixed dose PHAD-SE formulation in the research pharmacy. The Group A (LASSARAB 700rU dose), Group B (LASSARAB 1400rU), and HDCV are administered as 1 mL volume by intramuscular (IM) injection into the deltoid.

Group C will be administered as two LASSARAB 1400rU doses of 1 mL volume each by IM injection given into bilateral deltoids simultaneously. A normal saline placebo will be administered as 1 mL volume by IM injection in some HDCV control recipients to maintain blinding in Group C.

Safety, reactogenicity, and immunogenicity of the candidate LASSARAB+aPHAD-SE vaccine will be compared to a commercially available rabies vaccine, human diploid cell vaccine (HDCV, produced by the Merieux Institute and sold under the name “Imovax”), also administered in a two-dose series. Parameters of safety, reactogenicity, and immunogenicity will be reported by treatment group.

Study Duration: Approximately 15 months

Participant Duration: Approximately 13 months

Safety: This clinical study will use both a Safety Review Committee (SRC) and an Independent Safety Monitor (ISM). The SRC will consist of the PI, a DMID representative, and the Investigational New Drug (IND) sponsor Representative. The SRC will evaluate safety data after the first study vaccination from Cohorts 1-3 to assess safety of sentinel subgroup participants, provide sentinel subgroup safety data to the ISM for concurrence of SRC safety findings, and will notify the IND sponsor Representative of intent to proceed if no study Sentinel Subgroup

Halting Criteria are met (Appendix 1). Standardized dose escalation criteria and safety evaluations will be used.

The ISM will be an objective, medically qualified physician-scientist who is not involved with the conduct of the study. The ISM will be separate and independent of study personnel participating in this trial and should not have scientific, financial, or other conflicts of interest related to this trial. The primary responsibility of the ISM is to monitor participant safety. The ISM considers study-specific data as well as relevant background information about the disease, test agent, and target population under study. During scheduled reviews after sentinel subgroup vaccinations as well as at any time during the study when the SRC identifies that halting criteria may have been met, the ISM will evaluate the data and recommend appropriateness of further dosing. Any member of the SRC may request an ISM review at any time. The ISM will have the option to be unblinded to treatment group as needed and will have as a resource an unblinded statistician to aid in analyses of data. The decision to advance to the next dosing cohort will be documented and provided to the SRC. The ISM will be empowered to suspend (halt) the study, recommend amendments to the protocol, and/or to request further information for their review.

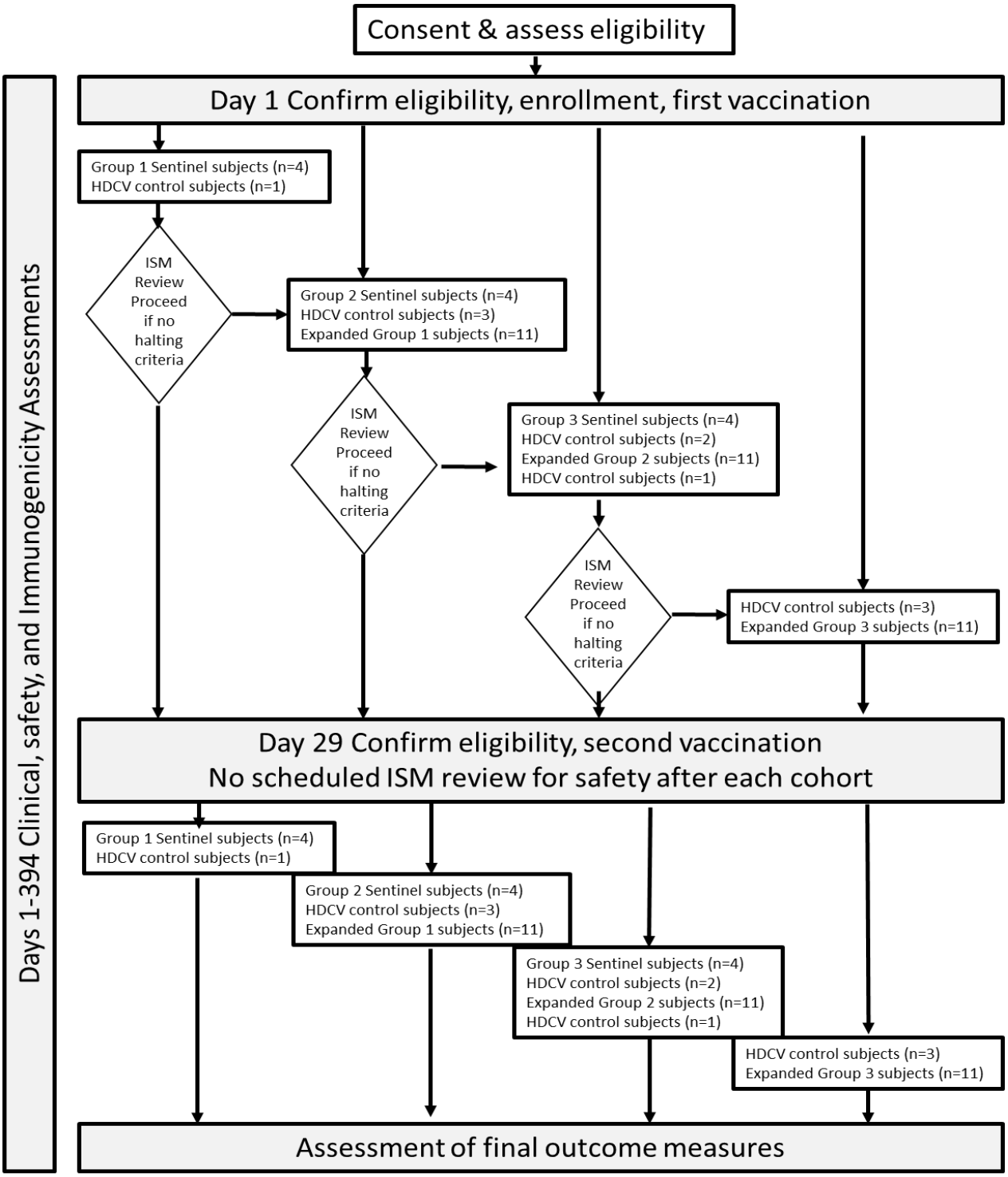
See Appendix 1 for Sentinel Subgroup Halting Criteria, Individual Halting Criteria, and General Study Halting Criteria. Further information about safety assessments is in Section 8.3, and descriptions of SRC and ISM procedures are in Section 10.1.6.

1.2 Schedule of Activities (SoA)

Procedures	Screening Study Visit 0	Vaccination #1 Study Visit 1 Day 1	Study Visit 2 Day 3 (±1)	Study Visit 3 Day 8 (±3)	Study Visit 4 Day 22 (±7)	Vaccination #2 Study Visit 5 Day 29 (±3)	Study Visit 6 Day 31 (±3)[18]	Study Visit 7 Day 36 (±3)	Study Visit 8 Day 61 (±3)	Study Visit 9 Day 121 (±14)	Study Visit 10 Day 210 (±14)	Study Visit 11 Day 394 (±14)	Unscheduled Visit[17]	Early Termination Visit[17]
Type of Visit	**Clinic**	**Clinic**	**Phone**	**Clinic**	**Clinic**	**Clinic**	**Phone**	**Clinic**	**Clinic**	**Clinic**	**Phone**	**Clinic**	**Clinic**	**Clinic**
Informed Consent[1]	X													
Review/Confirm Eligibility Criteria	X	X				X[18]								
Demographics	X													
Medical History[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications Review[3]	X	X	X	X	X	X	X	X	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]
Complete Physical Exam (including height and weight)[4]	X													
Targeted Physical Exam[5]		X[5]		X[5]		X[5]		X[5]	X[5]	X[5]		X[5]	X[5]	X[5]
Vital Signs[6]	X	X[6]		X		X[6]		X	X	X			X[5]	X[5]
Hematology/Chemistries[7]	X			X				X[18]	X[18]				X[5]	X[5]
HIV, HCV, HbsAg, rabies neutralization	X													
Serum Pregnancy Test[8]	X													
Urine Pregnancy Test[9]		X				X[18]								
Audiometry Test[10]	X	X			X				X			X	X	X
Immunology Blood		X[11]		X		X[11,18]		X	X	X		X	X[5]	X[5]
Study Vaccination		X				X[18]								
Vaccination Site Checks		X		X		X[18]		X[18]						
Dispense 7-day Diary Card e-[12]		X				X[18]								
Review 7-day Diary Card			X	X			X	X[18]					X[13]	X[13]
Solicited Adverse Events[14]			X	X			X	X					X[13]	X[13]
Unsolicited Adverse Events[15]		X	X	X	X	X	X	X	X				X[13]	X[13]
SAEs, MAAEs, NOCMCs, PIMMCs, and the AESI[16]		X	X	X	X	X	X	X	X	X	X	X	X	X

1. Prior to any study related procedures, participants will be provided information about the study and informed consent will be obtained from the participant.
2. Eligibility and medical history will be updated on the day of enrollment, before administration of study product.
3. Medications taken by the participant in the 60 days before enrollment will be recorded. At subsequent visits, updates to previous concomitant medications and additional medications taken in the interim will be recorded until Day 61 after which concomitant medications will only be recorded if used to treat an MAAE.
4. Physical examination will occur for all participants at Screening and will include general appearance and the following organs, organ systems and/or body areas: abdomen, heart, extremities, head, eyes, ears (including otoscopy), nose, and throat, lymph nodes, neurological, lungs, chest and skin.
5. Performed at investigator discretion.
6. Vital signs include pulse, systolic blood pressure, diastolic blood pressure, and oral temperature. On vaccination days, vital signs are performed prior to vaccination and at 30 minutes post vaccination. Vital signs meeting Grade 1 severity criteria (Appendix 5) and not clinically significant may be eligible as determined by the investigator.
7. Laboratory tests will include ALT, total bilirubin, creatinine, total WBC count, hemoglobin, and platelet count. For enrollment, values must be within normal limits or Grade 1 (Appendix 3) and not clinically significant as determined by the Investigator. Laboratory AEs are defined as abnormal safety labs collected from the time of vaccination through Day 61.
8. Serum Beta hCG for participants of childbearing potential.
9. Urine pregnancy test will be performed for all participants of childbearing potential within the 24 hours prior to study product administration. Result must be negative before study product can be administered.
10. Audiometry is scheduled to be performed four times: during the screening visit, prior to the second vaccination on Day 22, on Day 61, and on Day 394. Evidence of sensorineural hearing loss (SNHL) as assessed by quantitative audiometry at screening would exclude participation, and evidence of new onset SNHL before Day 29 would exclude receipt of the second vaccine dose. Evidence of new-onset SNHL after receipt of the first vaccination would be evaluated as a potential adverse event of special interest (AESI). The baseline exam may occur at any time from informed consent to immediately before first vaccine dose. Additional exams can be performed at the investigator's discretion.
11. Sample collection will occur prior to vaccination on Days 1 and 29. Left-over and additional blood specimens will also be retained and collected for future use (Appendix 2).
12. Participants will be trained on the use of the paper 7-day Diary Card. They will also be provided with a thermometer for daily temperature checks and a ruler to measure certain local reactogenicity events
13. If within relevant allowable time windows.
14. Solicited AEs will first be collected 30 minutes after administration of vaccine (immediate reactogenicity). Additional solicited AEs will be collected by the paper 7-day Diary Card for 7 days after each study vaccination.
15. Non-serious unsolicited AEs will be collected and recorded from Day 1 after administration of vaccine for all participants through Day 61.
16. SAEs, MAAEs, NOCMCs, PIMMCs, and the AESI, will be collected from Day 1, following vaccination, through the end of the study (Day 394).
17. Unscheduled Visits and Early Termination Visits may be conducted by phone or IRB-approved telehealth means if in-person visits are not feasible.
18. Not to be completed for those who did not receive Vaccination #2 but remain in the study for follow-up.

1.3 Study Schema



2. INTRODUCTION

2.1 Study Rationale

Lassa fever is a high mortality infectious disease that disproportionately affects low-income countries in West Africa.[1] There are currently no approved vaccines for Lassa fever in clinical use. The World Health Organization (WHO) has identified vaccines against Lassa fever as an unmet public health need.[7] This vaccine is proposed for disease prevention in Lassa fever endemic areas, where transmission is driven primarily by contact with infected rodent urine or feces. Additionally, it is proposed for use during Lassa fever outbreaks, in the mitigation of disease spread, including via person-to-person contact or nosocomial spread.

2.2 Background

2.2.1 Purpose of Study

Lassa fever is a zoonotic infection endemic in West Africa and is spread by the Lassa virus, an arenavirus causing hemorrhagic fever. Over 300,000 Lassa fever infections occur annually and while disease is often mild, in a subset of individuals disease is characterized by severe anemia and bleeding, encephalopathy, respiratory failure, and shock, and with high mortality. In some regions of West Africa, up to 15% of hospital admissions are secondary to Lassa fever, and an estimated 5,000 deaths occur annually. During epidemics of disease, case-fatality rates may reach as high as 50% in hospitalized patients. Approximately one-third of infected individuals will develop hearing loss regardless of disease severity, and in a proportion of patients, permanent deafness occurs.

Prevention of illness through vaccination is a critical goal in reducing the burden of disease from Lassa fever. While the antiviral ribavirin has shown some benefit in treatment, it is difficult to access in the regions where Lassa fever is endemic, and it must be started early in the disease course to be effective. There are currently no vaccines in clinical use for the prevention of Lassa fever.

This study proposes the evaluation of a novel, first-in-human Lassa fever vaccine based on the complete Lassa glycoprotein complex (GPC) antigen. The antigen (LASSARAB) will be presented on a genetically modified and attenuated rabies vector expressing both the rabies glycoprotein (GP) antigen and the Lassa GPC. The inactivated chimeric virus is delivered with a TLR-4-activating oil-in-water emulsion adjuvant (aPHAD-SE). Studies using this vaccine (called LASSARAB+aPHAD-SE) administered as a prime-boost series in mice and non-human primates, and then challenged with Lassa virus demonstrated significant protection against Lassa fever.[4,6,8-10] Given that the vaccine backbone is an attenuated and inactivated rabies virus expressing rabies GP, this vaccine will also be evaluated for immunogenicity against rabies virus.

2.3 Risk/Benefit Assessment

2.3.1 Known Potential Risks

LASSARAB +aPHAD-SE

This is the first study in humans of the investigational vaccine, LASSARAB +aPHAD-SE, and therefore risks are unknown. No clinical studies have been conducted.

Risks of study antigen (LASSARAB): Inactivated rabies virus has been used to vaccinate humans since 1978, and thus has a significant established history of manufacturing, safety, and efficacy.[4-6,8,10] The RABV-vectored vaccine used in this trial is inactivated and therefore its safety profile is anticipated to be similar. Local and systematic reactions from vaccination with rabies vaccine are common, generally mild, and self-limited.

Risks of study adjuvant (aPHAD-SE): The adjuvant SE is in vaccines in clinical use.[11-22] MPLA is in vaccines in clinical use.[11-22] Both agents are considered safe in vaccines. aPHAD is a variant of MPLA.

Risks of LASSARAB+aPHAD-SE on Pregnant Women: The possible effects of LASSARAB on a fetus or nursing infant are unknown.

Theoretical risk of sensorineural hearing loss (SNHL): SNHL has been identified in approximately 25% of people recovered from Lassa fever.[23] While SNHL has not been identified in clinical trials of Lassa virus vaccine candidates[10], there is a theoretical risk with LASSARAB+aPHAD-SE. Participants will undergo screening audiometry to exclude persons with clinically significant, pre-existing SNHL, and they will undergo after the first vaccine dose, after the second vaccine dose, and upon completion of the study to assess any changes from baseline. Further, audiometry can be performed for any participant by trained study staff in the event of concerns of changes in hearing. In the event of abnormal audiometry post-vaccination, participants will be referred for clinical evaluation and their medical records will be collected and reviewed. New onset SNHL is an adverse event of special interest (AESI) in this study.

HDCV

HDCV risks include local reactions (e.g., pain at the injection site, redness, swelling, induration), reported among the majority of recipients. Most local reactions were mild and resolved spontaneously within a few days.[24] Mild systemic reactions (e.g., fever, headache, dizziness, gastrointestinal symptoms) were reported in 6.8-55.6% of recipients.[24]

Immediate systemic hypersensitivity reactions are possible but are less likely during the primary vaccination series compared to booster vaccination.[24] Systemic allergic reactions have been associated with the presence of betapropiolactone-altered human albumin in HDCV and the development of antibodies to this allergen.[24] No deaths resulting from these reactions have been reported.

HDCV is contraindicated for anyone with a known life-threatening systemic hypersensitivity reaction to any component of the vaccine when used for preexposure prophylaxis.[24] Participants with a prior history of severe allergic reaction to any rabies vaccine or to any component of HDCV will be excluded from study enrollment. Should a severe allergic reaction occur immediately following vaccination, medications to treat such a reaction will be immediately available for administration according to standard guidelines at the study site.

The risk HDCV during pregnancy is not thought to outweigh the benefits in the setting of rabies exposure or high risk preexposure prophylaxis, but the risk-benefit balance of HDCV in the setting of pregnancy and low rabies risk is uncertain.[24] Several studies have shown no indication of increased incidence of abortion, premature births, or fetal abnormalities associated with rabies vaccination.[24]

General Vaccine Risks

Participants will be counseled on possible side effects following vaccination and followed closely in the immediate post-vaccination period and during the following week for assessment of moderate to severe local or systemic reactogenicity.

Some people get severe pain in the shoulder and have difficulty moving their arm after a vaccination has been given. This happens very rarely and can be prevented by assuring that the IM injection is done in the appropriate area of the deltoid muscle.

Syncope (fainting) can occur in association with administration of injectable vaccines. In the immediate post-vaccination period, all participants will be monitored in a sitting or lying position for 30 minutes following vaccination to help prevent fainting and injuries caused by a fall.

Blood Drawing

Drawing blood may cause transient discomfort and fainting. Fainting is usually managed by having the participant lie down. Bruising at the blood draw site may occur but can be prevented or lessened by applying pressure to the draw site for several minutes. Drawing blood may also cause infection. The use of aseptic techniques will reduce this risk. Risks for blood drawn may include anemia.

Risk of loss of privacy or confidentiality

Participants will be asked to provide, in a private setting, Personally Identifying Information (PII) and Protected Health Information (PHI). All attempts will be made to keep PII and PHI confidential within the limits of the law. However, there is a chance that unauthorized persons will gain access to a participant's PII or PHI. All hard copy research records will be kept in a locked file cabinet or maintained in a locked room at the participating Vaccine Treatment and Evaluation Unit (VTEU) site. Electronic files and access to the central clinical and laboratory websites at which study-related data are stored will be password protected. Only people who are involved in the conduct, oversight, monitoring, or auditing of this study will be allowed access to

the confidential information that is collected. Any publications from this study will not use information that will identify participants by name. Organizations that may inspect and/or copy research records for quality assurance and data analysis include groups such as National Institute of Allergy and Infectious Diseases (NIAID) and the Food and Drug Administration (FDA) and their contractors. They also include the Human Research Protections Office (HRPO) at the University of Maryland, Baltimore (UMB) and its IRB, and the Office of Accountability and Compliance (OAC) at UMB.

Unknown risks

There may be unknown risks, discomforts, or side effects.

2.3.2 Known Potential Benefits

Participation in this study provides no known direct benefit to the individual participants. Participants will be advised as part of the informed consent process that receipt of the comparator vaccine, HDCV, according to the study schedule is not sufficient to be considered to be protective against rabies virus or to have completed the pre-exposure prophylaxis (PrEP) vaccination series.

2.3.3 Assessment of Potential Risks and Benefits

This study may not benefit participants directly. As this is a first-in-human trial, it is unknown whether the study product, LASSARAB +aPHAD-SE, will help to protect participants from Lassa fever or rabies, or, if it does, how long that protection may last.

The immunogenicity comparator HDCV given at two doses is insufficient to prevent rabies virus infection.

Study risk is minimized by using a dose escalation procedure, as well as a sentinel subgroup approach within each dose group. Group safety reviews occur between sentinel and expanded subgroups.

While individual participants may not benefit from involvement in this study, their participation is crucial to the larger societal benefit of improved medical interventions. By participating in this study, participants are enabling the development of a potential advancement to address whether LASSARAB +aPHAD-SE may provide protection against Lassa fever.

3. OBJECTIVES AND ENDPOINTS

Refer to Section 1.1 for Study Objectives and Endpoints.

4. STUDY DESIGN

4.1 Overall Design

This is a phase 1, randomized, controlled, recipient- and observer-blinded, dose-escalation clinical trial to evaluate the safety, tolerability, and immunogenicity of LASSARAB+aPHAD-SE vaccine candidate compared to a licensed rabies virus vaccine control (HDCV), each administered as two intramuscular (IM) doses on Days 1 and 29 in adult participants aged 18 through 50 years. The trial will enroll up to 55 healthy participants. The study treatment groups are summarized in Table 1. If all 55 participants are enrolled and vaccinated, the randomization will be 3:3:3:2 of LASSARAB 700rU dose, LASSARAB 1400rU dose, LASSARAB 2800rU dose (2 injections of 1400rU), and HDCV comparator.

Participants will be recruited from the greater Washington/Baltimore Metropolitan Area. The trial will be conducted by a single center, the Center for Vaccine Development and Global Health (CVD) at the University of Maryland, Baltimore (UMB). Participants will be screened to determine eligibility for enrollment. Screening will include evaluations for general health, factors that may increase the risk to participants in the trial, and factors that could confound interpretation or execution of the study. Eligible participants will be enrolled and randomized to treatment group using block randomization for each cohort generated by the unblinded study statistician. Participants will then be vaccinated in a dose escalating process as shown in Table 2. The investigators, study staff (excluding vaccine administrators), and study participants will be blinded to the treatment each participant receives. Adverse events (AEs) will be assessed by blinded study clinicians for severity using relevant DMID toxicity tables and for the relationship of the event to the study product treatment.

For this trial, a conservative dose escalation design is used in which each treatment group of 15 vaccine recipients is split into two subgroups. The first subgroup, termed the “sentinel subgroup,” includes 4 vaccine recipients. The second subgroup, termed the “expanded subgroup,” includes the remaining 11 vaccine recipients. In each of the three initial treatment groups (Group A, Group B, and Group C), enrollment is paused for 7 days after vaccination of the sentinel subgroup for safety review.

Study participants will be divided into four vaccination cohorts.

- In Cohort 1, there will be 4 LASSARAB 700rU dose recipients (Group A sentinel subgroup) and 1 HDCV control recipient. If no Sentinel Subgroup Halting Criteria are met after 7 days of safety monitoring, an Independent Safety Monitor (ISM) will recommend proceeding to vaccinate Cohort 2.
- In Cohort 2, there will be 4 LASSARAB 1400rU dose recipients (Group B sentinel subgroup), 3 HDCV control recipients, and 11 LASSARAB 700rU dose recipients (Group A expanded subgroup). If no Sentinel Subgroup Halting Criteria are met after 7 days of safety monitoring, the ISM will recommend proceeding to vaccinate Cohort 3.
- In Cohort 3, there will be 4 recipients of two simultaneous injections of LASSARAB 1400rU dose product (Group C sentinel subgroup), 3 HDCV control recipients, and 11 single-injection LASSARAB 1400rU dose recipients (Group B expanded subgroup). If

no Sentinel Subgroup Halting Criteria are met after 7 days of safety monitoring, the ISM will recommend proceeding to vaccinate Cohort 4.

- In Cohort 4, there will be 3 HDCV control recipients, and 11 recipients of two simultaneous injections of LASSARAB 1400rU dose product (Group C expanded subgroup).

There will be no further planned ISM safety reviews for dose escalation after Cohort 4, although study investigators will continue to monitor for safety and apply relevant Individual Halting Criteria and General Study Halting Criteria and safety procedures when applicable. To maintain blinding of participants in Cohort 3 and 4, one dose of normal saline placebo will be administered simultaneously in the contralateral arm in some participants receiving HDCV control (See Table 2 for details).

Participants will be monitored for one year following the second study vaccination (through Day 394). Paper Diary Cards will be used to collect solicited and unsolicited AE information covering the 7-day period following each study vaccination. Safety laboratory analyses will be performed on Day 8 and Day 36 (7 days following each study treatment), as well as on Day 61. Blood samples will be obtained for immunological assays at Days 1, 8, 29, 36, 61, 121 and 394. Left-over and additional blood specimens will also be retained and collected for future use.

Unsolicited adverse events will be collected through Day 61 (32 days after the last study treatment). Only a subset of AEs will be collected beyond Day 61; these are serious adverse events (SAEs), medically-attended adverse events (MAAEs), new-onset chronic medical conditions (NOCMCs), potential immune-mediated medical conditions (PIMMCs), and an adverse event of special interest (AESI) – new onset sensorineural hearing loss (SNHL). SNHL will be assessed by audiometry at screening, after the first vaccine dose at Day 22, after the second vaccine dose at Day 61, upon completion of the study at Day 394, and at any time if the participant reports change in hearing or at the discretion of the Principal Investigator (PI). SAEs, MAAEs, NOCMCs, PIMMCs, and the AESI will be collected through Day 394 (the end of the study, approximately one year after the second study vaccination). See Section 7.1.5 for SNHL definitions and evaluation procedures and see Appendix 7 for the list of specific PIMMCs to be reported.

An interim analysis of the Primary and Secondary Endpoints will be performed with all data and samples collected through Day 61. These analyses will be summarized in tables by vaccine group and reported in an interim clinical study report (CSR). Data and studies from blood samples collected after Day 61 will be reported in separate CSRs. Assessed exploratory endpoints and data line listings will also be included in the final CSR.

4.2 Scientific Rationale for Study Design

For this Phase 1 first-in-human trial, a conservative dose escalation design will be used in which each treatment group of 15 vaccine recipients is split into two subgroups. The first subgroup,

termed the "sentinel subgroup," includes 4 vaccine recipients. The second subgroup, termed the "expanded subgroup," includes the remaining 11 vaccine recipients. In each of the three initial treatment groups (Group A, Group B, and Group C), enrollment is paused for 7 days after vaccination of the sentinel subgroup for safety review. This allows the opportunity to identify early vaccine-related AEs in this subgroup prior to exposing additional participants, a design that decreases the risk of multiple serious vaccine-related AEs compared to sequential vaccination of the entire dose group without halting. Vaccination will occur in cohorts including participants in other study treatment groups (HDCV control or dose groups that have already successfully completed sentinel safety reviews) to ensure vaccine assignment blinding by observers and participants. Unblinding can be done by the ISM to investigate any potential treatment-related AEs in the sentinel subgroups. The HDCV control group allows for comparisons between the LASSARAB+aPHAD-SE with a licensed rabies vaccine. Each is expected to elicit immune responses to rabies antigen, but only the LASSARAB+aPHAD-SE is expected to elicit immune responses to Lassa virus. The safety and tolerability profile for HDCV is well established.

4.3 Justification for Dose

The doses of LASSARAB+aPHAD-SE used in this Phase I clinical study are selected based on pre-clinical data. A vaccine candidate using 1400rU LASSARAB administered with TLR4 activating adjuvant, in SE, was given to nonhuman primates (NHPs) by IM injection at Days 1 and 29 and was found to be immunogenic and to generate high and persistent titers of antibodies against Lassa GPC.[4] No severe adverse events were observed in the NHPs monitored daily after immunization through one year post-immunization.[4] The same dose of vaccine candidate was found to highly suppress viremia on Lassa virus challenge in NHPs and to protect NHPs from death upon challenge. Thus, this trial will begin with ½ of the NHP dose (700rU antigen in 1 mL volume) and escalate as described to a 1400rU dose in 1 mL volume, and subsequently, if all safety criteria are met, to the highest dose of 2800rU, administered as two 1 mL injections of 1400rU each (Table 1). Each 1 mL volume will contain 5ug/mL aPHAD-SE.

5. STUDY POPULATION

This study will enroll healthy adult participants from the general population who meet eligibility criteria. Subject Inclusion and Exclusion Criteria must be confirmed by a study clinician licensed to make medical diagnoses. No exemptions are granted on participant Inclusion/Exclusion Criteria.

5.1 Inclusion Criteria

Refer to Section 1.1 for Study Inclusion Criteria.

5.2 Exclusion Criteria

Refer to Section 1.1 for Study Exclusion Criteria.

5.2.1 Exclusion of Specific Populations

This is a first-in-human study, to be conducted in a healthy adult population. There is no prior clinical experience with LASSARAB+aPHAD-SE. We are excluding adults older than 50 years, children and adolescents under 18 years of age, as well as persons who are pregnant, planning to become pregnant through Day 62, or who are breast-feeding.

5.3 Inclusion of Vulnerable Participants

Not Applicable

5.4 Lifestyle Considerations

During this study, participants are asked to:

- Participants of childbearing potential in a heterosexual relationship must agree to use of highly effective contraception beginning at the time of the screening visit through Day 61
- Refrain from donating blood through Day 61
- Refrain from enrolling in any other study with blood draws or any experimental agent or other intervention through the end of the study.
- Refrain from receiving any other vaccine through Day 61
- Refrain from receiving any live vaccine through Day 61
- Refrain from participating in another clinical trial or plan to enroll in another clinical trial during the study period.
- Must agree to inform the investigators if there are any potential rabies exposures or change in rabies risk for counseling about potential withdrawal from the trial for licensed rabies vaccination.

5.5 Screen Failures

Following consent and screening evaluations, the investigator or designee will review the inclusion/exclusion criteria and determine the participant's eligibility for the study and administration of the study product.

Participants who are found to be ineligible will be told the reason for ineligibility. Participants who are ineligible and not administered the study product will be replaced. Participants who withdraw, who are withdrawn from this study, or who are lost to follow-up after signing the ICF but before administration of the study product may be replaced.

Only the following information will be collected on screen failures: demographics (age, screen number, sex, ethnicity, and race) and reason for ineligibility.

For individuals who do not meet the criteria for participation in this study (screen failure) because of a laboratory value that is outside the range of eligibility, but the laboratory value is thought to be due to an acute condition or due to laboratory error, the abnormal laboratory

assessment may be repeated once. Similarly, for vital signs that fall outside of the range of eligibility, but the vital sign is thought be due to an acute condition or measurement error, the vital sign may be repeated once.

5.6 Strategies for Recruitment and Retention

5.6.1 Recruitment

Potential participants will learn about the study via IRB-approved recruitment strategies, including direct mailing, recruitment from an IRB-approved trial registry, internet advertisements, and local advertisements/flyers. Recruiting may begin with a brief IRB-approved telephone call between study staff and the potential participant. Information about the study will be presented to potential participants, and questions about their health and ability to comply with the study visit schedule will be asked of potential participants to presumptively determine eligibility. Information about the participant may be recorded from interviews or medical records. Appointments will be made for potential participants for further screening procedures.

5.6.2 Retention

Study retention strategies will include education and explanation of the study schedule and procedures during screening and enrollment visits and restriction of enrollment to persons who can attend all study visits. Participants will be reminded of subsequent visits during each visit, and study staff will contact participants prior to appointments. Study staff will contact participants who miss appointments to encourage them to return for completion of safety evaluations.

5.6.3 Compensation Plan for Participants

Participants may be compensated for their participation in this trial. Compensation will be in accordance with local IRB requirements, and subject to IRB approval. Reimbursements will be disbursed at specific timepoints during the study with the amount contingent on completing study procedures.

5.6.4 Costs

There is no cost to participants for the research tests, procedures, and study product while taking part in this trial. Procedures and treatment for clinical care may be billed to the participant, participant’s insurance or third party.

6. STUDY PRODUCT

6.1 Study Product(s) and Administration

6.1.1 Study Product Description

Product 1: LASSARAB+aPHAD-SE

The product is a Rabies-Vectored Monovalent Lassa Fever Vaccine (LASSARAB) with 3D-(6-acyl) Phosphorylated Hexaacyl Disaccharides (PHAD)-Stable squalene oil-in-water nanoemulsion (aPHAD-SE) adjuvant administered by IM injection. The LASSARAB vaccine consists of a chemically inactivated and genetically modified rabies virus (RABV) vector, expressing both the rabies glycoprotein (GP) antigen and the full Lassa glycoprotein complex (GPC) antigen. The parental RABV vaccine vector, BNSP, is a recombinant derivative of the SAD B19 RABV vaccine strain, which has been used as a live oral vaccine for wildlife in Europe. LASSARAB contains an Arg to Glu change at amino acid 333 of RABV G, which reduces viral neurotropism. Once the sequence is translated into a viral particle, it is then chemically inactivated with beta-propiolactone. The inactivated vaccine is delivered with a TLR-4-activating stable squalene oil-in-water nanoemulsion adjuvant, aPHAD-SE. The aPHAD adjuvant is a fully synthetic form of monophosphoryl lipid A (MPLA), specifically 3D-(6-acyl) PHAD®. SE is a stabilized nanoemulsion of squalene and water. The LASSARAB vaccine is administered in combination with the aPHAD-SE adjuvant formulation in a two-dose series. The LASSARAB vaccine is liquid and will be mixed with the aPHAD-SE formulation to produce one dose (1 mL) in the research pharmacy prior to administration.

In this trial, LASSARAB+aPHAD-SE will be administered in three different treatment dose groups: LASSARAB 700rU dose (Group A), LASSARAB 1400rU dose (Group B), or two simultaneous injections of LASSARAB 1400rU dose (for total LASSARAB dose of 2800rU) (Group C). The Group A and Group B vaccines will be delivered in a single IM injection of 1 mL vaccine product. The Group C vaccines will be delivered in two separate IM injections of the LASSARAB 1400rU dose formulation, each with a volume of 1 mL vaccine product.

Product 2: HDCV Comparator

HDCV (marketed as “Imovax®” and produced by Sanofi Pasteur SA) is a sterile, stable, freeze-dried suspension of rabies virus prepared from strain PM-1503-3M obtained from the Wistar Institute, Philadelphia, PA. The virus is harvested from infected human diploid cells, MRC-5 strain, concentrated by ultrafiltration and is inactivated by beta-propiolactone. The finished, freeze-dried vaccine is provided in a single dose vial containing no preservative. The potency of one dose (1 mL) of Imovax Rabies vaccine is equal to or greater than 2.5 international units of rabies antigen. Imovax Rabies is a vaccine indicated for pre-exposure and post-exposure prophylaxis against rabies. In the United States, the Advisory Committee on Immunization Practices (ACIP) recommends three IM injections of 1 mL each, one injection on Day 1, one on Day 8, and one either on Day 22 or 29. Imovax Rabies vaccine is approved for use in all age groups.

Product 3: Normal Saline Placebo

Sterile 0.9% sodium chloride for injection, USP, or normal saline, will be administered in IM injections simultaneously with HDCV in cohorts that contain Treatment Group C, Cohorts 3 and 4. The use of normal saline control allows maintenance of treatment assignment blinding in these

cohorts, given that Group C requires two IM doses given simultaneously.

6.1.2 Dosing and Administration

Treatment Group	Product Name	Antigen Dose	Adjuvant Dose	Route	Frequency of Administration	Duration of Therapy
A	LASSARAB+ aPHAD-SE	700rU	5µg	IM	D1, D29	N/A
B	LASSARAB+ aPHAD-SE	1400rU	5µg	IM	D1, D29	N/A
C	LASSARAB+ aPHAD-SE	1400rU per injection (2 injections)	5µg per injection (2 injections)	IM	D1, D29	N/A
D	HDCV	≥2.5 IU rabies antigen	N/A	IM	D1, D29	N/A

Note: Treatment Group C will receive two simultaneous injections of the LASSARAB 1400rU dose vaccine. Therefore, each participant in treatment Group C will receive a total 2800rU LASSARAB and 10µg aPHAD-SE. Some Group D participants will receive an injection of normal saline placebo simultaneous to HDCV to maintain blinding of Group C.

6.1.3 Dose Escalation

For this Phase 1 first-in-human trial, a conservative dose escalation design will be used. LASSARAB+aPHAD-SE will be evaluated in three different treatment dose groups, Group A, Group B, and Group C in a stepwise dose escalation process. Details of the dose escalation are in Table 2, Sections 1.1, and Section 4.1.

6.1.4 Dose Modifications

Not applicable

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Acquisition and Accountability

- Product 1:
    - Component 1: LASSARAB (IDT Biologika GmbH)
    - Component 2: aPHAD-SE (Curia)
    - Component 3: Normal Saline buffer (Fisher)
- Product 2: HDCV (Fisher)
- Product 3: Normal Saline (Fisher)

Product 1 Component 1 (LASSARAB) will be distributed by IDT Biologika GmbH. Product 1 Component 2 (aPHAD-SE) will be distributed by Curia. Product 1 Component 3, Product 2, and Product 3 will be procured by the University of Maryland, Baltimore from Fisher BioServices. Records will be maintained that document receipt, release for dosing, disposal, or return to the

IND sponsor.

Additional procurement of specific products will be done by University of Maryland, Baltimore. This includes but may not be limited to, mixing vials, syringes, needles and shipping supplies for this study.

Accountability: After receipt of the study products, the PI is responsible for study product distribution and disposition and has ultimate responsibility for study product accountability. The PI may delegate to the research pharmacist responsibility for study product accountability. The research pharmacist will be responsible for maintaining complete records and documentation of study product receipt, accountability, preparation/dilution, dispensation, storage conditions, and final disposition of the study product(s). All study product(s), whether administered or not, must be documented on the appropriate study product accountability record or dispensing log. The IND sponsor's monitoring staff will verify the participating site's study product accountability records and dispensing logs per the site monitoring plan. Refer to the protocol-specific Manual of Procedures (MOP) for details on storing study products.

Unused study products will be retained until study conclusion or until accountability via verification of inventory or monitoring has occurred and written notification stating retention is no longer required is received from the IND sponsor, as applicable per the site's Standard Operating Procedures (SOPs).

6.2.2 Formulation, Appearance, Packaging, and Labeling

Manufacturing and packaging of the formulation ingredients will be performed for the study by the UMMC Investigational Drug Pharmacy (heretofore referred to as the "research pharmacy") and will be documented in conformity with Good Manufacturing Practice (GMP) per instructions. The study products will be labeled according to manufacturer or regulatory specifications and include the statement "Caution: New Drug – Limited by Federal (or United States) law to investigational use."

Product 1: LASSARAB+aPHAD-SE (Active Product)

LASSARAB+aPHAD-SE is formulated with LASSARAB at a concentration of 6990 rel. U/mL and aPHAD-SE at a concentration of 25µg/mL in a sterile normal saline diluent to produce a final dose volume of 1 mL. One dose of LASSARAB+aPHAD-SE will be formulated with 700rU or 1400rU of LASSARAB antigen and 5µg of aPHAD-SE. Treatment Group C will receive two simultaneous vaccinations of the LASSARAB 1400rU dose product in bilateral arms (for a total LASSARAB dose of 2800rU). Single dose vials will be produced by the research pharmacy and stored at room temperature for use within 4 hours. The drug product will be supplied in 1 mL syringes for administration. The final prepared drug product is a colorless, slightly cloudy suspension with presence of white particles. Table 3 has specifics of the formulation for the three dose levels.

Product 2: HDCV Comparator

The study will use licensed HDCV as a comparator product. HDCV is sold as Imovax Rabies Vaccine. The licensed HDCV vaccine is supplied as single-use vials and will be procured through commercial sources with storage and administration in accordance with the manufacturer's recommendations. The product is pink to red color after reconstitution.

Product 3: Normal Saline

Sterile 0.9% sodium chloride for injection, USP, or normal saline, is a sterile, nonpyrogenic, isotonic solution; each mL contains sodium chloride 9 mg. It contains no bacteriostatic agent, antimicrobial agent, preservatives, or added buffer and is supplied only in single-dose containers. The solution may contain hydrochloric acid and/or sodium hydroxide for pH adjustment (pH 5.3, range 4.5-7.0). Normal saline will be supplied as single-use vials. The product is clear.

Table 3. Formulations of LASSARAB +aPHAD-SE by Treatment Group

Treatment Group	Product	Antigen Dose	Adjuvant Dose	Volume	Route	Frequency of Administration	Therapy Duration
A	LASSARAB+ aPHAD-SE	700rU	5µg	1 mL	IM	D1, D29	N/A
B	LASSARAB+ aPHAD-SE	1400rU	5µg	1 mL	IM	D1, D29	N/A
C	LASSARAB+ aPHAD-SE	1400rU per injection (2 injections)	5µg per injection (2 injections)	1 mL (2 injections)	IM	D1, D29	N/A

Note: Treatment Group C will receive two simultaneous injections of the LASSARAB 1400rU dose vaccine Therefore, each participant in treatment Group C will receive a total 2800rU LASSARAB and 10µg aPHAD-SE. Some Group D participants will receive an injection of normal saline placebo simultaneous to HDCV to maintain blinding of Group C.

6.2.3 Product Storage and Stability

Product 1: LASSARAB+aPHAD-SE (Active Product)

LASSARAB and aPHAD-SE drug product in storage vials will be characterized for stability prior to IND submission to FDA. LASSARAB vials will be stored at ≤-65°C while aPHAD-SE vials will be stored 2-8°C. Products will be thawed at ambient temperature prior to mixing – LASSARAB for 30 minutes and aPHAD-SE for 15 minutes. Upon mixing, the drug product will be kept at room temperature for up to four hours before use.

Product 2: Licensed HDCV (Comparator)

The freeze-dried, commercial presentation of HDCV is stable if stored in the refrigerator between 2°C and 8°C. Upon reconstitution, if should be administered promptly.

6.2.4 Preparation

Product 1: LASSARAB+aPHAD-SE

Preparation of LASSARAB+aPHAD-SE will be performed by the research pharmacy and will be documented in conformity with Good Manufacturing Practice (GMP) per instructions provided in the Study Manual of Procedures.

The individual participant vaccines are prepared from bulk and stored in capped, glass vials at room temperature prior to administration within 4 hours. The vaccine will be prepared in two dose levels: LASSARAB 700rU dose, LASSARAB 1400rU dose, each adjuvanted with 5 µg aPHAD-SE in normal saline. A third dose level (LASSARAB 2800rU Dose) will be accomplished by administering two separate IM injections of the LASSARAB 1400rU Dose formulation, each with a volume of 1 mL vaccine product. The individual drug product components as shown in Table 3 will be used in the formulation of the LASSARAB+aPHAD-SE treatments.

Product 2: Licensed HDCV

The HDCV commercial presentation package contains a vial of freeze-dried vaccine, a syringe containing diluent, and a sterile reconstitution needle. Preparation of HDCV will be performed by the research pharmacy and will be documented in conformity with Good Manufacturing Practice (GMP) per instructions provided in the Study Manual of Procedures. The individual participant vaccines will be reconstituted following instructions in the product package insert in the study vaccination clinic immediately prior to administration. Measures to Minimize Bias: Randomization and Blinding

6.2.5 Treatment Assignment Procedures

Participants will be assigned to receive either one of three doses of LASSARAB+aPHAD-SE or HDCV comparator depending upon the cohort into which they enroll (Table 2). Some Cohort 3 and 4 participants will receive an injection of normal saline placebo simultaneous to HDCV to maintain blinding of Treatment Group C. Study product will be administered within four hours of its preparation.

6.2.6 Randomization and Blinding

Upon verification of study eligibility at the Day 1 visit, participants will be randomized according to Table 2. Because this is a dose escalation trial, our study has four stages with one cohort receiving vaccines at each stage. Up to 55 participants will be randomized to one of the four treatment groups at an assignment ratio depending on the escalation stage. If all participants proceed to vaccination, the final vaccine assignment ratio will be 3:3:3:2 of LASSARAB 700rU dose, LASSARAB 1400rU dose, LASSARAB 2800rU dose, and HDCV comparator.

Participants will receive a study vaccination on Days 1 and 29. Randomization will be generated by the study statistician using block randomization for each cohort separately. All randomized trial subjects will be blinded to their treatment allocation.

6.2.7 Blinding and Masking Procedures

Trial personnel receiving, storing, dispensing, preparing, and administering the trial study product will be unblinded. All other trial personnel, including the investigator and investigator staff, will be blinded to trial treatment allocation. In particular, the individuals who evaluate participant safety and immunogenicity will be blinded. Because LASSARAB+aPHAD-SE or HDCV have different appearances, the trial treatment will be administered in a manner that maintains the blinding. For this study blinding tape will be applied to the syringe by unblinded study staff before product administration. The participants, the study personnel who perform study assessments after administration, data entry personnel at the sites, and laboratory personnel performing immunologic assays will be blinded to treatment assignment.

The investigator will assign the responsibility of the unblinded dispensers/administrators to trial personnel who will not participate in the evaluation of any trial endpoint. To ensure adequate coverage, at least two unblinded dispensers/administrators will be assigned per trial site. Members of the trial site personnel or clinic pharmacy should fulfill these roles. The investigator and trial site personnel other than the unblinded dispensers/administrators must not be allowed to know the treatment allocation of any trial participant and must not be allowed to see the investigational product container contents. In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded trial treatment allocation records at the site(s) to verify that randomization/dispensing has been done accurately.

The SRC will receive blinded data in aggregate by cohort. At scheduled timepoints after sentinel subgroup vaccinations, and if Individual Halting Criteria and General Study Halting Criteria are met at other times during the study, the SRC will refer safety review to the ISM who may choose to be unblinded to individual study treatment assignments, as needed, to adequately assess safety issues.

6.3 Unblinding

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a trial subject's treatment allocation is warranted. Trial participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the trial sponsor's representative before unblinding a trial participant's treatment allocation unless this could delay further management of the trial participant. If a participant's treatment allocation is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form (CRF). Decision on trial continuation of unblinded trial subjects will be made between investigator and sponsor's representative on a case by case basis**.**

6.4 Study Intervention Compliance

Vaccination of participants will be performed by a member of the clinical research team who is licensed to administer the study product, and the administration will be documented on the

Treatment Administration Record and entered into the electronic Case Report Form (eCRF).

6.5 Concomitant Therapy

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the electronic Case Report Form (eCRF) are concomitant prescription medications, over-the-counter medications and supplements.

All concomitant medications taken within 60 days prior to signing the ICF will be reviewed with participants to determine stability of chronic diseases and eligibility and recorded on the data collection forms/source documentation. Concomitant medications will be reviewed at every study visit through the end of the study.

Participants should not have current use of any medications that may be associated with impaired immune responsiveness (Exclusion Criterion 2).

Participants should not have any allergy treatment with antigen injections within 60 days before first vaccination or that are planned through the end of the study (Exclusion Criterion 3).

Participants of childbearing potential in a heterosexual relationship must agree to use highly effective contraception beginning at the time of the screening visit through Day 61 (Inclusion Criterion 6).

Participants should not have immunoglobulins and/or any blood products within the 60 days before first vaccination or that are planned through the end of the study (Exclusion Criterion 4).

Participants should not have received rabies vaccine or an antibody therapeutic product for treating rabies or a Lassa fever vaccine any time before the first planned study vaccination (Exclusion Criterion 9).

Participants should not have received another experimental agent or other intervention within 60 days before first vaccination or have plans to do so before the end of the study (Exclusion Criterion 10).

Participants should not have received or have plans to receive any other vaccine in the 2 weeks prior to vaccination/enrollment through Day 61 (Exclusion Criterion 11).

Participants should not have received or have plans to receive any live vaccine in the 4 weeks prior to signing ICF through Day 61 (Exclusion Criterion 12).

6.5.1 Rescue Medicine

Not applicable

7. STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Halting Criteria and Discontinuation of Study Intervention

7.1.1 Study Halting Criteria

Sentinel Subgroup Halting Criteria, Individual Halting Criteria, and General Study Halting Criteria are in Appendix 1**.** The primary responsibility of the ISM is to monitor participant safety. The ISM will review safety data at scheduled timepoints after sentinel subgroup vaccinations. Should any of the Sentinel Subgroup Halting Criteria, Individual Halting Criteria, or General Study Halting Criteria be met, the study will be paused, and the ISM will evaluate the data and recommend appropriateness of further dosing. The ISM will have the option to unblind by treatment group as needed and will have as a resource an unblinded statistician to aid in analyses of data. See Section 10.1.6 for details of SRC and ISM responsibilities.

7.1.2 Individual Halting Criteria

This study includes two doses of investigational product. Individual participant halting criteria that would preclude a second dose in the event of safety events associated with the first dose are included to ensure participant safety. These criteria are in Appendix 1.

7.1.3 Criteria for redosing

Not applicable

7.1.4 Follow up for participants that discontinued study intervention

Discontinuation from study vaccine receipt does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study schedule of activities. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an AE. See Section 1.2 for data to be collected and follow-up evaluations.

7.1.5 Follow up for Participants with a Suspicion for Sensorineural Hearing Loss

Participants will undergo scheduled evaluations for SNHL at screening as part of eligibility assessments, after the first vaccination on Day 22, after the second vaccination on Day 61, and upon completion of the trial on Day 394. Audiometry will also be performed if the participant reports change in hearing or any time at the investigator's discretion. Evaluation of SNHL as an AESI will follow Brighton Collaboration guidance.[23] The screening tablet audiometer used in the vaccine clinic will be compliant with Brighton guidelines. To follow up on abnormal in-clinic tests after enrollment, we will use formal diagnostic sound booth audiometry completed by a licensed audiologist and evaluation by an otologist for SNHL diagnosis. SNHL evaluation will be detailed in the MOP.

The threshold for normal hearing is -10 to 15 dB in children and adults.[23] Hearing loss is present when hearing acuity drops below 30 dB loss.[23] The Brighton Collaboration states that the

definitive diagnosis of SNHL requires two components:

- Hearing loss of at least 30 dB in three sequential frequencies in the standard pure tone audiogram, and
- A physical examination to exclude conductive hearing loss.[23]

During screening, we will exclude persons with a baseline a hearing level greater than 15 dB in three sequential frequencies by tablet audiometry if physical examination confirms conductive hearing loss. We will also exclude persons with hearing level of greater than or equal to 20 dB at any single frequency by tablet audiometry if physical examination confirms conductive hearing loss. If there is an easily reversible cause of conductive hearing loss (such as earwax removal), tablet audiometry and/or diagnostic sound booth audiometry may be repeated to assess eligibility.

New onset SNHL after vaccination will use the Brighton Collaboration definition of SNHL for the AESI definition.[23] In the event of abnormal screening tablet audiometry after vaccination, all participants will be evaluated promptly (within 2 business days) by a co-investigator otologist for confirmatory testing and possible initiation of standard of care treatment for sudden SNHL, all of which will be documented in the clinical database. Participants will be informed that these evaluations are done for safety assessments as part of the clinical trial. In the event of adverse events requiring continued monitoring, further assessments, or medical care, participants will be referred to appropriate health care facilities. Once SNHL is confirmed by diagnostic sound booth audiometry and otologist evaluation, AESI reporting will be done according to Section 8.4.8.

Results of screening tablet audiometry and diagnostic sound booth audiometry will be confirmed by the PI or designated clinician licensed to make medical diagnoses and listed on Form FDA 1572. Screening tablet audiometry and diagnostic sound booth audiometry readouts will be uploaded into the study database.

In the event of true medical emergencies, stabilizing care will be administered, and arrangements will be made to dispatch the participants for emergency care. Relevant information including vaccine allocation, study records, clinical data, clinical assessments, and medical recommendations will be made available to the participants and their healthcare providers. Records will be sought from the healthcare provider encounters to inform AESI data collection and reporting.

7.2 Participant Withdrawal from the Study and Replacement

Participants are free to withdraw from participation in the study at any time upon request. An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Participant becomes pregnant prior to study product dosing (Section 8.4.12))
- Study non-compliance that in the opinion of the investigator poses an increased risk or compromises the validity of the data.

- If any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
- If the participant meets an exclusion criterion for participation in the study (either newly developed or not previously recognized) that precludes further study participation.
- Medical disease or condition, or new clinical finding(s) for which continued participation, in the opinion of the investigator, might compromise the safety of the participant, interfere with the participant's successful completion of this study, or interfere with the evaluation of responses.
- Participant lost to follow-up.

If the participant agrees, every attempt will be made to follow all AEs through resolution.

Participants who withdraw, or are withdrawn from this study, or are lost to follow-up after signing the ICF and after administration of the study product will not be replaced. Participants who withdraw, are withdrawn from this study, or are lost to follow-up after signing the ICF but before administration of the study product may be replaced.

The reason for participant discontinuation or withdrawal from the study will be recorded in the electronic Case Report Form (eCRF).

7.3 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the study site staff.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1 Screening Procedures

Screening procedures may be performed up to 60 days prior to enrollment (Day-60 to Day -1), with the exception of screening audiometry which may be performed any time prior to the first study vaccination. After informed consent the following assessments are performed to determine eligibility and obtain baseline data:

- Collection of demographic data
- Take a focused medical history, including the following information:
    - Assess childbearing status
    - History of any chronic medical conditions.
    - History of any medication allergies including history of hypersensitivity to any component of the study products.
    - Concomitant medications taken within 60 days prior to signing the ICF will be reviewed with participants to determine stability of chronic diseases and eligibility.

  - Assess allergy history
  - Assess vaccination, immunoglobulin or other blood products, antigen injection history within 60 days prior to signing the ICF and planned receipt
- Participants of childbearing potential in a heterosexual relationship should be counseled to either practice true abstinence or use at least one primary form of contraception until 30 days after receipt of the study product. Participants of childbearing potential must have a negative serum HCG pregnancy test at screening and a negative urine HCG pregnancy test within 24 hours of administration of study product.
- A physical examination will be performed on all participants, by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the PI or sub-investigator, to include general appearance and the following organs, organ systems and/or body areas: abdomen, heart, extremities, head, eyes, ears (including otoscopy), nose, and throat, lymph nodes, neurological, lungs, chest and skin. Height and weight measurement (calculation of BMI).
- Vital signs measurement (including pulse, systolic blood pressure, diastolic blood pressure, and oral temperature).
- Blood for laboratory evaluations.
  - Serology at screening: HIV 1 and 2 antigen/antibody, Hepatitis B surface antigen, Hepatitis C antibody, rabies neutralization.
  - Hematology studies at screening: white blood cells (WBC) count, hemoglobin, and platelets.
  - Chemistry studies at screening: ALT, total bilirubin, creatinine.
- Baseline audiometry

Clinical screening laboratory evaluations will be performed in Frostburg, Maryland by Aeon Technologies Laboratories and/or locally at the University of Maryland Medical Center laboratories. Urine pregnancy tests and audiometry will be performed by research staff. The volume of venous blood to be collected is presented in Appendix 2.

The overall eligibility of the participant to participate in the study will be assessed when all screening values are available. Study participants who qualify will be enrolled and entered into the Data Coordinating Center (DCC) and all others will be registered as screen failures.

8.1.1 Procedures to be Followed in the Event of Abnormal Laboratory Test Values or Abnormal Clinical Findings

If a physiologic parameter, (e.g., vital signs) is outside of the protocol-specified range, then the measurement may be repeated once if, in the judgment of the investigator, the abnormality is the result of an acute, short-term, rapidly reversible condition (e.g., stress, anxiety, or “white coat syndrome”). A physiologic parameter may also be repeated if there is a technical problem with the measurement caused by malfunctioning, or an inappropriate measuring device (i.e., inappropriate-sized blood pressure cuff).

A participant may be re-screened if there is a transient disease status (e.g., participant complained of a "cold or fever" and met a temporary delaying enrollment criterion of acute illness or fever), or if a protocol eligibility criterion that is not met at the initial time of screening, will be met by rescreening at a later date (e.g., a medication taken within exclusionary window at the time of first screening that would not be within exclusionary window at a later rescreen).

Results of screening laboratory testing will be discussed with the participant. Participants will be provided the results of any abnormal clinical laboratory results and will be referred to their primary healthcare provider. Screening laboratory values that are outside the range of eligibility but are thought to be due to an acute condition or due to laboratory error may be repeated once. Research laboratory results will not be provided to the participant.

No participant may be screened more than twice due to a screening failure result as defined above.

8.2 Immunogenicity Assessments

8.2.1 Immunogenicity Evaluations

Measurement of anti-Lassa virus antibodies measured by ELISA at Day 1, 8, 29, 36, and 61.

Measurement of anti-rabies virus antibodies measured by ELISA and RFFIT at Day 1, 8, 29, 36, and 61.

See Appendix 2 for venipuncture volumes.

8.2.2 Exploratory Assessments

- Measurement of anti-Lassa virus antibodies measured by ELISA at Day 121 and 394.
- Measurement of anti-rabies virus antibodies measured by ELISA and RFFIT measured by ELISA at Day 121 and 394.

In addition to the exploratory assessments, participants will consent to retention of unused serum specimens and to collection of additional blood specimens (including human peripheral blood mononuclear cells [PBMCs]) for storage and potential future use research.

See Appendix 2 for venipuncture volumes.

8.3 Safety and Other Assessments

Study procedures, timelines, and acceptable time windows are specified in Section 1.2. A study clinician licensed to make medical diagnoses and listed on the 1572 will be responsible for all trial-related medical decisions.

Specimens for clinical screening and safety laboratory evaluations will be transported from the clinic sites to the respective site's certified clinical laboratories or on-site certified laboratories for analysis. Specimens for immunology will be transported for processing, storage, transport

and/or analysis to CVD research laboratories.

Ongoing Abstinence and Contraceptive Counseling

Participants of childbearing potential in a heterosexual relationship should be counseled to use highly effective contraception through Day 61.

Physical Examination

A physical exam will be conducted at screening (Day -60 to -1) by a licensed study clinician. A targeted physical exam will be performed at in-person visits (Days 1, 8, 29, 36, 61, 121, and 394) at the investigator's discretion.

Vital Signs

Vital signs will be assessed at screening (Day -60 to -1) and at in-person visits (Days 1, 8, 29, 36, 61, 121, and 394). Vital signs will include pulse, systolic blood pressure, diastolic blood pressure, and oral temperature. On vaccination days (Day 1 and Day 29), vital signs are performed prior to vaccination and again at 30 minutes post vaccination.

Audiometry

As described in Section 7.1.5, tablet audiometry will be performed by study staff at screening (Day -60 to -1), Day 22, Day 61, Day 394, and at the investigator's discretion. Abnormal tests will be confirmed by formal diagnostic sound booth audiometry and otologist evaluation within 2 business days.

Clinical Laboratory Evaluations

- Serology at screening: HIV 1 and 2 antibody, Hepatitis B surface antigen, Hepatitis C antibody, rabies neutralization
- Hematology (at screening and Days 8, 36, and 61 and any unscheduled visit or early termination visit at the investigator's discretion): white blood cells WBC, hemoglobin, and platelets
- Chemistry studies (at screening and Days 8, 36, and 61 and any unscheduled visit or early termination visit at the investigator's discretion): ALT, TBILI, creatinine
- Serum Beta hCG pregnancy test for participants of childbearing potential at screening
- Urine pregnancy test will be performed for all participants of childbearing potential within the 24 hours prior to study product administration (Days 1 and 29)

8.3.1 Scheduled Phone Visits for Safety Assessment

Safety assessment visits by phone are conducted three days after each study vaccination (Days 3 and 31). During these visits, participants will be asked whether there has been any change in their medical history, and their concomitant medications will be reviewed. The paper Diary Card will be reviewed for potential AEs, and participants will be reminded to complete it daily

through 7 days post-vaccination. Participant training on the use of the paper Diary Card, the thermometer, and the ruler will be reinforced. Participants will also be reminded to contact the study personnel for safety concerns or other questions, and they will be directed to contact phone numbers in the paper Diary Card. Solicited AEs, unsolicited AEs, MAAEs, NOCMCs, PIMMCs, SAEs, and changes in hearing (potentially SNHL) will be assessed. Participants will be reminded of their scheduled in-person appointments for Days 8 and 36. If there are concerns about an ongoing AE by either the study staff member or the participant, an in-person unscheduled visit can be scheduled for further assessment.

8.3.2 Procedures to be Followed in the Event of Abnormal Laboratory Test Values or Abnormal Clinical Findings

The PI or designated clinician licensed to make medical diagnoses and listed on Form FDA 1572 is responsible for recording all AE/SAEs that are observed or reported during this study, regardless of relationship to the study product. AE/SAEs, abnormal laboratory test values or abnormal clinical findings will be collected, assessed, documented, reported, and followed appropriately, using a local laboratory as necessary. In determining eligibility, refer to Section 5.1 and Section 5.2.

8.3.3 Unscheduled Visit

If the investigator deems the reaction warrants further evaluation or intervention, the investigator will give further instructions on the proper course of action, including a return to the clinic for immediate evaluation at an unscheduled visit if appropriate. The study will preferentially conduct an unscheduled visit in-person, but a visit by phone is acceptable when necessary.

8.3.4 Early Termination Visit

Should the participant withdraw or be withdrawn or terminated from this trial, the study team will request a final in-person visit for an evaluation, to include a review of changes in medical history, concomitant medications, review for potential AEs (including MAAEs, NOCMCs, PIMMCs, AESIs, SAEs) and possible targeted physical examination, tablet audiometry, vital signs, and laboratory evaluations, and blood collection for study immunology assays at the discretion of the investigator. Depending upon the time of the early termination visit, the participant will receive abstinence and contraceptive counseling.

8.4 Adverse Events and Serious Adverse Events

8.4.1 Definition of Adverse Events (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)). An AE can therefore be any unfavorable and unintended sign (including an increase in grade in an abnormal laboratory finding), symptom, or disease temporally associated with the use of

medicinal (investigational) product. Clinical laboratory AEs are defined as laboratory abnormalities with a grade level increase in clinical laboratory values per protocol toxicity tables.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the severity of any pre-existing medical condition increases, it should be recorded as an AE.

Adverse events can be further divided into solicited AEs and unsolicited AEs. Solicited AEs are those for which the study team will specifically query the participant whether they occurred.

Unsolicited AEs are those events that the participant reports occurring without being queried about the specific event. All AEs will be assessed for severity and relationship to study intervention.

All AEs, solicited and unsolicited, will be captured on the appropriate data collection form. Information to be collected for AEs includes event description, date of onset, assessment of severity, relationship to study product and alternate etiology (assessed only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as an investigator), date of resolution, seriousness and outcome. AEs occurring during the trial collection and reporting period will be documented appropriately regardless of relationship.

Laboratory test abnormalities are documented on the laboratory form and not recorded as a separate AE eCRF but the relationship, clinical significance, and grade will be noted on the laboratory form.

AEs will be followed through resolution.

8.4.1.1 Solicited Adverse Events

Each participant will be given a 7-day paper Diary Card, a thermometer, and a measuring device. Participant will use the diary to record their highest temperature, local and systemic symptoms, and any new concomitant medications daily for 7 days after each product administration. Subjects will be provided training on paper Diary Card completion and proper usage of the thermometer to measure temperature and the ruler to measure injection site symptoms. Completion of paper Diary Card training will be noted in the source documents. The paper Diary Card will be transcribed into the study database and stored in the subject file for monitoring purposes.

Solicited AEs will be collected through the 7-day paper Diary Cards and will include anticipated local and systemic AEs for which consistent collection of information is desired. This may include:

- Common and expected events according to the available knowledge about the product
- Specific events of concern that should be ascertained on every participant

- Solicited AEs as noted in protocol toxicity tables, as well as measured temperature and size of certain local reactogenicity events will be collected from each participant on Days 1-7 via the paper Diary Cards.

The participant paper Diary Card will be reviewed by a clinician for accuracy and completeness at follow-up visits. Study clinicians will review the paper Diary Card entries and severity assessments with the participants. The severity grading scale will be reviewed, and the participants will be asked to confirm that that their recorded symptom severity accurately aligned with the severity grading scale. Participants will be given the opportunity to revise their symptoms if they believe that they errored in their self-assessment of severity. Clinicians will follow any solicited symptoms that are ongoing after 7 days until they have resolved.

Participants using a paper Diary Card will be encouraged to contact the clinic as soon as possible for any moderate or severe side effects that they experience in the 7 days post product administration. A study clinician may contact the participant by phone if any moderate or severe side effect is reported. Study clinician mobile phone and back-up phone numbers will be provided in the event the participant has questions or concerns after clinic hours.

8.4.1.2 Unsolicited Events

All AEs spontaneously reported by the participant and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures must be recorded in the source document. All reported unsolicited AEs are graded in accordance with the protocol toxicity tables.

8.4.1.3 Special Reporting of Adverse Events

Not applicable

8.4.2 Definition of Serious Adverse Events

An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or IND sponsor, it results in any of the following outcomes (21 CFR 312.32 (a)):

- death
- a life-threatening adverse event
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include

allergic bronchospasm requiring intensive treatment in an emergency room or at home, convulsions that do not result in inpatient hospitalization, etc.

All SAEs, as with any AE, will be assessed for severity and relationship to study intervention. All SAEs will be recorded on the appropriate SAE data collection form and eCRF.

All SAEs will be followed through resolution by a licensed study clinician (for IND studies, a physician listed on the Form FDA 1572 as the Principal Investigator or sub-investigator).

All SAEs will be reviewed and evaluated by IND sponsor and will be sent to the ISM (periodic review unless related), and the IRB/IEC.

8.4.2.1 Suspected Unexpected Serious Adverse Reactions (SUSAR)

A SUSAR is any SAE where a causal relationship with the study product is at least reasonably possible but is not listed in the Investigator Brochure (IB), Package Insert, and/or Summary of Product Characteristics.

8.4.3 Classification of an Adverse Event

The determination of seriousness, severity, and causality will be made by an on-site investigator who is qualified (licensed) to diagnose AE information, provide a medical evaluation of AEs, and classify AEs based upon medical judgment. This includes but is not limited to physicians, physician assistants, and nurse practitioners.

8.4.3.1 Severity of Event

All AEs or SAEs will be assessed for severity, according to the FDA Guidance for Industry "Toxicity Grading Scales for healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (Appendix 3, Appendix 4, Appendix 5, and Appendix 6).

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- Mild (Grade 1): Events that are usually transient and may require only minimal or no treatment or therapeutic intervention. The event generally does not interfere with the participant's usual activities of daily living.
- Moderate (Grade 2): Events that are usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe (Grade 3): Events interrupt usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. Severe events are usually incapacitating.

AEs characterized as intermittent require documentation of onset and duration of each episode. The start and stop date of each reported AE will be recorded on the appropriate data collection

form and eCRF. Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of intensity.

8.4.3.2 Relationship to Study Intervention

For each reported adverse reaction, the PI or designee must assess the relationship of the event to the study product using the following guideline:

- Related – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- Not Related – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

8.4.4 Time Period and Frequency for Event Assessment and Follow-Up

For this study:

- Solicited AEs will be collected from vaccination on Day 1 and Day 29 through 7 days, and they will be reviewed on Day 8 and Day 36.
- Non-serious unsolicited AEs will be collected from Day 1 through Day 61.
- Clinical laboratory AEs will be assessed on Day 8, Day 36, and Day 61.
- MAAEs, SAEs, NOCMCs, PIMMCs, and the AESI (sensorineural hearing loss) will be collected from the Day 1 through the end of the study (Day 394).

Non-serious unsolicited AEs and clinical laboratory AEs may fall within the allowable time window noted in Section 1.2.

8.4.5 Adverse Event Reporting

8.4.5.1 Investigators Reporting of AEs

Information on all AEs should be recorded on the eCRF. All clearly related signs, symptoms, and results of diagnostic procedures performed because of an AE should be grouped together and recorded as a single diagnosis. If the AE is a laboratory abnormality that is part of a clinical condition or syndrome, it should be recorded as the syndrome or diagnosis rather than the individual laboratory abnormality. Each AE will also be described in terms of duration (start and stop date), severity, association with the study product, action(s) taken, and outcome.

8.4.6 Serious Adverse Event Reporting

8.4.6.1 Investigators Reporting of SAEs

Any AE that meets a protocol-defined serious criterion must be submitted immediately (within 24 hours of site awareness) on an SAE form to the IND sponsor, the SRC, and the ISM.

In addition to the SAE form, select SAE data fields must also be entered into the DCC system. Please see the protocol-specific MOP for details regarding this procedure.

Other supporting documentation of the event may be requested by the IND sponsor and should be provided as soon as possible. The site will send a copy of the SAE report(s) to the ISM (as deemed necessary) when they are provided to the IND sponsor. The IND sponsor will review and assess the SAE for regulatory reporting and potential impact on study participant safety and protocol conduct.

At any time after completion of the study, if the PI or appropriate sub-investigator becomes aware of an SAE that is suspected to be related to study product, the principal investigator or appropriate sub-investigator will report the event to the IND sponsor.

8.4.6.2 Regulatory Reporting of SAEs

Following notification from the PI or appropriate sub-investigator, the IND sponsor will report any SUSAR in an IND safety report to the FDA. The IND sponsor will report to the FDA any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the IND sponsor's initial receipt of the information. If the event is not fatal or life-threatening the IND safety report will be submitted within 15 calendar days after the IND sponsor determines that the information qualifies for reporting as specified in 21 CFR Part 312.32. Relevant follow up information to an IND safety report will be submitted as soon as the information is available. Upon request from FDA, the IND sponsor will submit to the FDA any additional data or information that the Agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request. SAEs that are not SUSARs will be reported to the FDA at least annually in a summary format which includes all SAEs.

For US-licensed vaccines such as HDCV: Established in 1990, the Vaccine Adverse Event Reporting System (VAERS) is a national early warning system to detect possible safety problems in US-licensed vaccines. VAERS is co-managed by the Centers for Disease Control and Prevention (CDC) and the FDA. VAERS accepts and analyzes reports of AEs (possible side effects) after a person has received a vaccination. Anyone can report an AE to VAERS. Healthcare professionals are required to report certain AEs and vaccine manufacturers are required to report all AEs that come to their attention.

VAERS is a passive reporting system, meaning it relies on individuals to send in reports of their experiences to CDC and FDA. VAERS is not designed to determine if a vaccine caused a health problem, but is especially useful for detecting unusual or unexpected patterns of AE reporting that might indicate a possible safety problem with a vaccine. This way, VAERS can provide CDC and FDA with valuable information that additional work and evaluation is necessary to further assess a possible safety concern.

Link to VAERS https://vaers.hhs.gov/.

8.4.7 Reporting Events to Participants

Not applicable

8.4.8 Adverse Events of Special Interest

Adverse Events of Special Interest (AESIs) are a pre-defined subset of AEs that may be required to be collected at the request of the regulatory agency, industry partner, DMID, or IND sponsor and is meant to address a specific safety concern. Any AESI that meets serious criteria must be submitted immediately (within 24 hours of site awareness) on an SAE form to the IND sponsor, the SRC, and the ISM.

In this study, new onset SNHL is considered an AESI. The evaluation of SNHL is detailed in Section 7.1.5.

All AESIs are assessed, recorded, and followed as described above. In addition, the AESI will be reported on an SAE form to the IND sponsor.

8.4.9 Medically-Attended Adverse Events

For each unsolicited AE experienced, the participant will be asked if he/she had received medical attention, defined as hospitalization, an emergency room visit or an otherwise unscheduled visit to or from medical personnel for any reason. AEs characterized by such unscheduled medical care will be designated as Medically-Attended Adverse Events (MAAEs) and will be reported in the DCC system.

8.4.10 New-Onset Chronic Medical Conditions

New-Onset Chronic Medical Conditions (NOCMCs) are defined as any new ICD-10 diagnosis (10th revision of the International Statistical Classification of Diseases and Related Health Problems) that is applied to the participant during the course of the study, after receipt of the study agent, that is expected to continue for at least 3 months and requires continued health care intervention. NOCMCs will be reported in the DCC system.

8.4.11 Potentially Immune-Mediated Medical Conditions

PIMMCs constitute a group of AEs that includes diseases which are clearly autoimmune in etiology and other inflammatory and/or neurologic disorders which may or may not have autoimmune etiologies. A PIMMC is any new ICD-10 diagnosis corresponding to the list of relevant diagnoses in Appendix 7 during the course of the study and after receipt of the study agent.

8.4.12 Reporting of Pregnancy

Pregnancies occurring in study participants will be reported via DCC system on the Pregnancy Report form. If the pregnant participant is agreeable, venous blood samples for safety and serological assays will still be collected per protocol; however, large volume blood samples for

cellular immunological assays will be discontinued. Efforts will be made to follow all pregnancies reported during the course of the study to pregnancy outcome.

8.5 Adverse Unanticipated Problems (UP)

8.5.1 Definition of Unanticipated Problems (UP)

The Department of Health and Human Services (DHHS) OHRP considers UP involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.5.2 Unanticipated Problem Reporting

The investigator will report UPs to the reviewing IRB and to the DCC and the PI. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.
- To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:
- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the DCC/IND sponsor within 24 hours of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC/IND sponsor within 2 weeks of the investigator becoming aware of the problem.

8.5.3 Reporting Unanticipated Problems to Participants

Not applicable

9. STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

There are no hypothesis tests pre-specified for this Phase I study, although some inferential statistics such as 95% confidence levels will be calculated to supplement the descriptive statistics provided for outcome measures. Any potential hypothesis testing will be considered exploratory and will be detailed in a separate statistical analysis plan (SAP). Details about planned tables, figures, and data listings will be presented in a separate SAP.

9.2 Sample Size Determination

The sample size is chosen without the intention that group differences will be detected with a sufficient power but is consistent with FDA guidance. A sample size of 55 is selected, with 15 persons in each of the three dose groups (Treatment Groups A, B, and C) for LASSARAB+aPHAD-SE and 10 persons in the HDCV control group (Treatment Group D). Table 4 indicates the probability of observing one or more safety events for a single group (N=10 or 15) and for all enrolled subjects (N=55).

Table 4. Probability to Detect One or More Safety Events

	Number of Subjects		
Event rate	**10**	**15**	**55**
10% -- Very Common	0.651	0.794	0.997
1% -- Common	0.096	0.140	0.425
0.1% -- Uncommon	0.010	0.015	0.054
0.01% -- Rare	0.001	0.001	0.005

9.3 Populations for Analyses

- The Intent-to-Treat (ITT) population will consist of all randomized participants who are vaccinated.
- The Modified Intention-to-Treat (mITT) population will include participants in the ITT population with the following exclusions of data:
    - Data from participants determined to be ineligible at baseline
    - Data from any visit that occurs out of window as defined in the Schedule of Activities
    - Data from all visits subsequent to major protocol deviations, as defined in the SAP, that could affect the validity of later data, such as:
        - Receipt of immunosuppression or any medications that may be associated with impaired responsiveness
        - Receipt of any non-study investigational drug/investigational vaccine/licensed vaccine as defined in the exclusion criteria
    - Data are available for a particular analysis.

The ITT population will be used for all analyses of AEs and reactogenicity. Immunogenicity analyses will be done in the mITT population.

9.4 Statistical Analyses

The primary clinical database for this study will consist of safety data including solicited reactogenicity events, unsolicited events, and abnormal laboratory values, as well as baseline/demographic data. There are two planned analyses. A first analysis (Interim Analysis) will occur after Day 61. After all participants have completed Day 61, fields from instruments needed for the interim analysis will be cleaned and there will be a database freeze to ensure data integrity. After the freeze, a snapshot of the data will be downloaded and used for the interim analysis. This database freeze will include fields from the following instruments: Demographics, Inclusion/Exclusion Criteria, Vaccine Administration, Reactogenicity Assessment, Laboratory Results and Adverse Events. After clinical database through Day 61 freeze and receipt of secondary endpoint immunogenicity data, a set of topline tables will be generated by the study statistician, including summaries of clinical safety and secondary immunogenicity data by treatment group. The topline report will be made available to the study team for planning subsequent trials and may be presented in a public forum or used for publication in collaboration with the PI. These analyses will be considered final and will be included in the CSR. Once the last participant has completed the final visit, the remaining clinical database (Day 61 through the end of the study) will be cleaned, monitored, and locked. At the time of database lock, access will be restricted to read-only to prevent further modification.

The CSR, comprised of the final analyses of safety and available immunological data, will be subsequently completed. The final CSR will be completed when all primary and secondary safety, clinical, and immunological endpoint data are available. Any available data from the exploratory endpoints at the time of compilation of the final CSR may also be included.

Additional exploratory endpoint data may be included in an addendum to the CSR, publication of manuscript(s), or other report.

A formal SAP, which will elaborate on the analyses described here and describe any changes to the planned analyses, will be developed and finalized before performing any of these analyses (with the exception of SRC/ISM reviews of descriptive safety analyses).

In addition to the descriptive analyses of study data for SRC/ISM review, an interim analysis is planned for the ongoing study to allow for an early assessment of the immunogenicity of the study vaccine and to aid in decision-making regarding future studies after Day 61 is completed for all participants. This analysis would not affect the conduct of this trial via early stopping.

Additional details on the planned interim analysis are given in Section 9.4.5.

9.4.1 General Approach

The non-missing sample size, mean, standard deviation, and the minimum, median, interquartile range, and maximum will be summarized as a descriptive analysis for all continuous variables. Categorical variables will be descriptively summarized by frequencies and percentages of observed levels, based on the observed data. Titers will be summarized with geometric means (GMTs), first across technical replicates to compute one value for each individual sample (where applicable) and then applied again across participants within the same group.

In general, summaries will be presented by treatment group and compared across groups using ANOVA F-test or Kruskal-Wallis H test for continuous variables and chi-square test or Fisher's exact test for categorical variables. All tables will be annotated with the total sample size relevant to that table, including any missing observations. The analysis sample for each exhibit will be clearly indicated. 95% confidence intervals will be computed for binary variables, where applicable.

Safety Analysis

The primary objective of the study is to assess the safety of a single dose of the study vaccination, as determined by the incidence of solicited reactogenicity events, unsolicited serious and non-serious AEs, SAEs, MAAEs, NOCMCs, PIMMCs, the AESI, and clinical laboratory AEs.

Safety objectives will be assessed in the ITT population. All summaries will be provided by treatment actually received. Solicited local and systemic reactogenicity events will be summarized via the number and percentage of participants reporting each event, and any solicited reactogenicity event, through 7 days post-vaccination. These will be tabulated by severity and any severity. 95% confidence intervals (CIs) for the probability of each event occurring collectively across any severity level post-vaccination will be computed for each group. Severity will be determined as described in Section 8.4.3.1.

Non-serious unsolicited AEs through Day 61 will be summarized by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC), MedDRA preferred term and severity at the end of the study in the final CSR. SAEs, MAAEs, NOCMCs, PIMMCs, and AESIs reported through the end of the study (one year after the second study vaccination) will be summarized similarly. Clinical laboratory AEs are defined as a grade level increase in clinical laboratory values (per protocol toxicity tables) and will be summarized separately. For unsolicited events, summaries regarding relationship to study vaccine will also be provided, as described in Section 8.4.3.2. AE rates will be compared among the treatment groups as well as between the control group and the three study treatment groups combined.

AEs and abnormal clinical laboratory results, including clinical laboratory AEs, will be presented in data listings.

9.4.2 Secondary Immunogenicity Analysis

The secondary objectives of the study are the following:

1) To assess the serum antibody response of LASSARAB+aPHAD-SE vaccine as compared to licensed HDCV control. These responses will be assessed via Lassa- glycoprotein complex (GPC) antigen antibodies measured by ELISA at Day 1, 8, 29, 36, and 61 per treatment group.
2) To assess the antibody response of LASSARAB+aPHAD-SE vaccine as compared to licensed HDCV control as measured by rabies GP antigen antibodies as measured by IgG ELISA and RFFIT test at Days 1, 8, 29, 36, and 61 per treatment group.

9.4.3 Exploratory Immunogenicity Analyses

Exploratory objectives of the study include:

- To assess the serum antibody response of LASSARAB+aPHAD-SE vaccine as compared to licensed HDCV control. These responses will be assessed via Lassa- glycoprotein complex (GPC) antigen antibodies measured by ELISA at Days 121 and 394 per treatment group.
- To assess the antibody response of LASSARAB+aPHAD-SE vaccine as compared to licensed HDCV control as measured by rabies GP antigen antibodies as measured by IgG ELISA and RFFIT test at Days 121 and 394per treatment group.

For each analysis, the GMT and corresponding 95% confidence intervals will be presented for applicable endpoints by treatment group and study day. For post-baseline time points, the geometric mean fold rise (GMFR) from baseline and corresponding 95% confidence intervals will be presented by treatment group. Seroconversion is defined as > 4 fold rise in antibody titer at any time point as compared to baseline with the minimum titer for seroconversion defined as four times the lower limit of quantification (LLOQ). The LLOQ for the assay will be determined as part of assay qualification. When an antibody titer at baseline is below LLOQ, it will be assigned a value 50% of the LLOQ to enable the calculation of fold rise. Details of the immunogenicity analyses will be included in the SAP.

9.4.4 Baseline Descriptive Statistics

Baseline and demographic characteristics will be summarized by treatment group, with summary statistics for all enrolled participants as described in Section 9.4.1. These characteristics will include age, sex, ethnicity, and race.

9.4.5 Planned Interim and Early Analyses

9.4.5.1 Interim Safety Analyses

Two groups will review safety for this study: The SRC and the ISM. They are described in detail in Section 10.1.6.

9.4.5.2 Interim Immunogenicity

As described in Section 9.4, an interim analysis focused primarily on immunogenicity will be conducted while the study is ongoing.

9.4.6 Sub-Group Analyses

There are no planned sub-group analyses for this study due to small sample sizes.

9.4.7 Tabulation of Individual Participant Data

Safety data, reactogenicity data, and immunogenicity data will be presented in listings at the end of study in the final CSR, as described in Section 9.4.1.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory, Ethical, and Study Oversight Considerations

Each institution engaged in this research will hold a current Federalwide Assurance (FWA) issued by the OHRP for federally funded research.

The investigator will submit applicable information to the IRB/IEC on which it relies for the review, to conduct the review in accordance with 45 CFR 46, ICH E6(R2) GCP, and as applicable, 21 CFR 56 (Institutional Review Boards) and 21 CFR 50 (Protection of Human Subjects), other federal, state, and local regulations. The IRB/IEC must be registered with OHRP as applicable to the research. IND sponsor must receive the documentation that verifies

IRB/IEC-approval for this protocol, associated informed consent documents, and upon request any recruitment material and handouts or surveys intended for the participants, prior to the recruitment and enrollment of participants.

Any amendments to the protocol or consent materials will be approved by the IRB/IEC before they are implemented. IRB/IEC review and approval will occur at least annually throughout the enrollment and follow-up of participants. The investigator will notify the IRB/IEC of deviations from the protocol and reportable SAEs, as applicable to the IRB/IEC policy.

10.1.1 Informed Consent Process

Informed consent is a process that is initiated prior to an individual agreeing to participate in a trial and continuing throughout the individual's trial participation. Before any study procedures are performed, informed consent will be obtained and documented. Participants will receive a concise and focused presentation of key information about the clinical trial, verbally and with a written consent form. The key information about the purpose of the study, the procedures and experimental aspects of the study, study interventions/products, probability for random assignment to treatment groups, risks and discomforts, the expected duration of the participant's participation in the trial, any expected benefits to the participant, and alternative treatments and procedures that may be available to the participant. The explanation will be organized and presented in lay terminology and language that facilitates understanding why one might or might

not want to participate.

Participants will receive an explanation as to whether any compensation and any medical treatments are available if injury occurs, and, if so, what they consist of, or where further information may be obtained. Participants will be informed of the anticipated financial expenses, if any, to the participant for participating in the trial, as well as any anticipated prorated payments, if any, to the participant for participating in the trial. They will be informed of whom to contact (e.g., the investigator) for answers to any questions relating to the research project.

Information will also include the foreseeable circumstances and/or reasons under which the participant's participation in the trial may be terminated. The participants will be informed that participation is voluntary and that they are free to withdraw from the study for any reason at any time without penalty or loss of benefits to which the participant is otherwise entitled.

Participants will be informed that records identifying the participant will be kept confidential, and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available and, if the results of the trial are published, the participant's identity will remain confidential. Participants will be informed whether private information collected from this research and/or specimens will be used for additional research, even if identifiers are removed.

Participants will be informed that the monitor(s), auditors(s), IRB, NIAID, and regulatory authority(ies) will be granted direct access to the participant's original medical records for verification of clinical trial procedures and/or data without violating the confidentiality of the participant, to the extent permitted by the applicable laws and regulations, and that, by signing a written informed consent form, the participant is authorizing such access.

Participants will be allowed sufficient time to consider participation in this research trial and have the opportunity to discuss this trial with their family, friends or legally authorized representative, or think about it prior to agreeing to participate.

Informed consent forms will be IRB-approved and participants will be asked to read and review the consent form. Participants must sign the ICF prior to starting any study procedures for this trial. Once signed, a copy of the ICF will be given to the participant(s) for their records. New information will be communicated by the PI to participants who consent to participate in this trial in accordance with IRB requirements. The informed consent document will be updated, and participants will be re-consented per IRB requirements, if necessary.

10.1.1.1 Requirements for Permission by Parents/Guardians and Assent by Children (in case of a minor)

Not applicable

10.1.1.2 Other Informed Consent Procedures

Not applicable

10.1.2 Study Termination and Closure

Section 7.1 describes the temporary halting of the study.

This study may be prematurely terminated if there is sufficient reasonable cause, including but not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Halting criteria met and it is deemed unsafe to proceed with further dosing
- Insufficient compliance with protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Decision by regulatory authorities

If the study is prematurely terminated, the PI will promptly inform study participants, the IRB and regulatory authorities as applicable. Study participants will be contacted, as applicable, and be informed of changes to the study visit schedule. The PI will assure appropriate follow-up for the participants, as necessary.

The IND sponsor will notify regulatory authorities as applicable.

10.1.3 Confidentiality and Privacy

Participant confidentiality is strictly held in trust by the participating investigators, their staff, the IND sponsor and their agents. This confidentiality is extended to cover clinical information relating to participants, test results of biological samples and all other information generated during participation in the study. No identifiable information concerning participants in the study will be released to any unauthorized third party. When a participant's hepatitis B, hepatitis C, or HIV screening result is positive, the result will be reported to the Maryland Department of Health. The test results will be kept confidential to the extent permissible under the law.

Participant confidentiality will be maintained when study results are published or discussed in conferences.

The study monitor, other authorized representatives of the IND sponsor, representatives of the IRB, and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

All source records including electronic data will be stored in secured systems in accordance with institutional polices and federal regulations.

All study data and research specimens that leave the site (including electronic transmission of data) will be identified by a coded number that is linked to a participant through a code key maintained at the clinical site. The code key, including names or readily identifiable information is kept confidential and will not be transmitted off site.

As this research is funded by the NIH, it is covered by NIH policy which effectively issues the research a Certificate of Confidentiality (COC). By this policy, researchers cannot be forced to disclose or provide, in any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding, the name of such individual or any such information, document, or biospecimen that contains identifiable, sensitive information about the individual and that was created or compiled for purposes of the research, unless such disclosure or use is made with the consent of the individual to whom the information, document, or biospecimen pertains.

The Certificate cannot be used to resist a demand for information from personnel of the US Government that is used for auditing or evaluation of federally funded projects, like this study, or for information that must be released in order to meet the requirements of the FDA.

A Certificate of Confidentiality does not prevent the participant from voluntarily releasing information about themselves or their involvement in this research. If any person or agency obtains a written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

The Certificate of Confidentiality does not prevent the researchers from reporting without the participant's consent, information that would identify the participant as a participant in the research project regarding matters that must be legally reported including child and elder abuse, sexual abuse, or wanting to harm themselves or others.

The release of individual private information or specimens for other research will only occur if consent was obtained from the individual to whom the information, document, or biospecimen pertains, or for the purposes of other research that the release is in compliance with applicable Federal regulations governing the protection of human subjects in research.

10.1.4 Future Use of Stored Specimens and Data

Secondary Human Subject Research is the re-use of identifiable data or identifiable biospecimens that were collected from some other ''primary'' or ''initial'' activity, such as the data and samples collected in this protocol. This section will detail the samples and data available for secondary research. Any use of the sample or data, however, will be presented in a separate protocol and require separate IRB approval.

10.1.4.1 Samples for Secondary Research

To participate in this study, eligible participants must consent to the storage and use of leftover and extra samples and associated data for the purpose of future research. Some extra specimens will be collected specifically for the purposes of secondary research. Samples designated for secondary research use may be used in additional assessments that may include but are not limited to, evaluation of antibody responses, functional antibody assays, evaluation of cellular immune response, and evaluation of the innate immune response. These specimens might be used in new or different immunological laboratory tests, to provide information for the

development of new vaccines or therapeutics, or for the study of Lassa virus or other infections. Specimens will be coded. Any future testing laboratory will not have access to the code, and therefore will not be able to identify study participants. Diagnostic genetic testing on these samples will not be performed. The specifics of this secondary research testing will be in a separate protocol and will be reviewed by an IRB. Samples will not be sold for commercial profit. Although the results of any future research may be patentable or have commercial profit, participants will have no legal or financial interest in any commercial development resulting from any future research.

Risks are associated with the additional volume of blood collected, such as anemia. Risks for loss of privacy and confidentiality are described below. Hence, the following types of samples will be stored and used for secondary research:

- Residual biological specimens - Any leftover primary research sample after laboratory testing is completed per protocol.
- Repository research sample - Samples will be collected with the participant's consent in this protocol with the intent to store for additional research (i.e., samples collected beyond those needed for primary research including whole blood for isolation of peripheral blood mononuclear cells) and will be used in future studies.

Samples will be stored indefinitely at an IND sponsor-designated storage facility.

Secondary research with coded samples and data may occur; however, participant confidentiality will be maintained as described for this protocol. An IRB review of the secondary research using coded specimens is required. Residual/Repository Research Samples, upon written request and approval from IND sponsor and any approvals required by the site, may be shared for secondary research with investigators at the participating site, with researchers at other institutions, or company-designated research laboratories. The samples will not be sold or used directly for production of any commercial product. Reports from secondary research will not be kept in the participants' health records or shared with participants, unless required by law. The participant's decision for secondary research can be changed at any time by notifying the study doctors or nurses in writing. If the participant changes his/her decision, the samples will be destroyed if the samples have not been used for research or released for a specific research project.

10.1.4.2 Data Sharing for Secondary Research

Data from this study may be used for secondary research. All of the individual participant data collected during the trial will be made available after deidentification. The Statistical Analysis Plan and Analytic Code will also be made available. This data will be available immediately following publication, with no end date. The data will be made available to researchers who provide a methodologically sound proposal. The data will be available for any purpose outlined in the approved proposal. Proposals should be directed to the IND sponsor. To gain access, data requestors will need to sign a data access agreement.

10.1.5 Key Roles and Study Governance

The IND sponsor of this study is Dr. Wilbur Chen of CVD, UMB. Decisions related to the study will be made by the protocol team, which includes the PI, DMID (the Funding organization), and the IND sponsor. The PI is listed on the cover page. Other study team members and roles are listed in the protocol-specific MOP.

10.1.6 Safety Oversight

This clinical study will use both a Safety Review Committee (SRC) and an Independent Safety Monitor (ISM). The SRC will consist of the PI, a DMID Representative, and the IND sponsor Representative. The SRC will evaluate safety data after the first study vaccination for each of the Cohorts 1-3 to assess safety of sentinel subgroup participants, provide sentinel subgroup safety data for ISM for concurrence of SRC safety findings, and will notify the IND sponsor Representative of intent to proceed if no study halting criteria are met (Appendix 1). Ad hoc reviews may also be called for by the investigators, IND sponsor, the SRC, or the ISM. Decisions are dependent on the failure to meet halting criteria when the required follow-up data are available. The SRC deliberations may occur by teleconference, videoconference, or email.

The SRC will review all available blinded safety data needed for dose escalation decisions. The SRC will determine whether halting criteria may have been met and seek ISM review. If the ISM agrees that halting criteria were not met, they will provide the SRC with a recommendation to proceed with dose escalation. If the ISM determines that halting criteria have been met, the study will be halted for further review by the ISM.

The ISM will be an objective, medically qualified physician-scientist who is not involved with the conduct of the study. The ISM will be separate and independent of study personnel participating in this trial and should not have scientific, financial, or other conflicts of interest related to this trial. The primary responsibility of the ISM is to monitor participant safety. The ISM considers study-specific data as well as relevant background information about the disease, test agent, and target population under study. During scheduled reviews after sentinel subgroup vaccinations as well as at any time during the study when the unblinded SRC identifies that halting criteria may have been met, the ISM will evaluate the data and recommend appropriateness of further dosing. If the unblinded SRC determines that halting criteria were not met, the ISM will be provided relevant study safety data for review and potential concurrence.

Any member of the SRC may request an ISM review at any time. The ISM will have the option to be unblinded to treatment group as needed and will have as a resource an unblinded statistician to aid in analyses of data. The decision to advance to the next dosing cohort will be documented and provided to the SRC. The ISM will be empowered to suspend (halt) the study, recommend amendments to the protocol, and/or to request further information for their review. If the ISM determines that the study data have met the criteria necessary to continue from a sentinel subgroup to expanded subgroup cohort or to begin a subsequent cohort, the ISM will notify the

SRC of the determination.

If the SRC or any of its members is unable to determine that the criteria necessary to continue to an expanded subgroup cohort or to begin a subsequent cohort have been met, or if halting criteria have been met, the ISM will be asked to review the data for independent assessment. Any SRC member can request an ISM review at any time.

Procedures for the SRC and ISM reviews will be detailed in the SRC Charter. See Appendix 1 for Sentinel Subgroup Halting Criteria, Individual Halting Criteria, and General Study Halting Criteria. Further information about safety assessments is in Section 8.3.

10.1.7 Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable. Clinical Monitoring also ensures conduct of the trial is in compliance with the currently approved protocol/amendment(s), International Council for Harmonisation, Good Clinical Practice, and with applicable regulatory requirement(s) and IND sponsor requirements.

Monitoring for this study will be performed by a representative of the IND sponsor. Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports. Monitoring visits will include, but are not limited to, review of regulatory files, accountability records, eCRFs, informed consent forms, medical and laboratory reports, site study intervention storage records, training records, and protocol and GCP compliance. Site monitors will have access to each participating site, study personnel, and all study documentation according to the site monitoring plan. Study monitors will meet with site principal investigators to discuss any problems and outstanding issues, and they will document site visit findings and discussions.

10.1.8 Quality Assurance and Quality Control

To ensure the reliability of study data, each site will develop a Clinical Quality Management Plan (CQMP). The CQMP will describe:

- Routine internal quality control (QC) and quality assurance (QA) activities
    - For the purposes of measuring, documenting and reporting study conduct, protocol adherence, human subjects' protections, and reliability of the protocol-driven data collected;
- A process for addressing in a timely manner any data quality issues (i.e., collecting, recording and reporting data), systemic issues (i.e., protocol conduct, non-compliance, human subject protections), and implementation of Corrective and Preventive Actions (CAPA) procedures.

The PI will implement QC procedures beginning with the data entry system and generate data QC

checks that will be run on the database. Any missing data or data anomalies will be communicated to the PI and clinical team for prompt clarification and resolution.

10.1.9 Data Handling and Record Keeping

10.1.9.1 Data Collection and Management Responsibilities

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

The site will maintain appropriate medical and research records in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of participants. The site will permit authorized representatives of the DMID and its designees, the IND sponsor and its designees, and appropriate regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress. These representatives will be permitted access to all source data and source documents, which include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, participants' paper Diary Cards or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and participant files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

This study uses direct data entry for the participating clinic site and the eCRFs serve as the source documents for data collected. Data will be entered electronically over the Internet by site study staff into REDCap, developed and maintained by the SDCC.

Participants will use a paper Diary Card. Participants will enter data into the paper Diary Card and review them with clinic staff during scheduled postvaccination phone calls (Days 3 and 31). Participants will also be asked to bring their paper Diary Card to postvaccination clinic appoints (Days 8 and 36) to review with study staff. The paper Diary Card is not considered source data. After clinic staff review and save the paper Diary Cards, the data will be entered into REDCap as source.

Clinical (including, but not limited to, AE/SAEs, concomitant medications, medical history, vital signs, ECG data, physical assessments, and clinical laboratory values) will be entered into eCRFs via a 21 CFR Part 11-compliant internet data entry system provided by the SDCC. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate.

Site staff who are delegated the responsibility by the study PI will be the data originators for clinical data entered directly into the eCRF. A list of all authorized data originators, including site staff, will be included on the Study Personnel/Signature Responsibility List.

Data collection is the responsibility of the study personnel at the participating clinical study site under the supervision of the principal investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. During the study, the principal investigator must maintain complete and accurate documentation for the study. The data coordinating center for this study will be responsible for data management, quality review, analysis, and reporting of the study data.

The IND sponsor is responsible for review of data collection tools and processes, and review of data and reports.

Adverse events will be coded according to the MedDRA dictionary Version 26.1.

At the end of the study, a copy of all datasets including annotated case report forms and data dictionary will be provided to the IND sponsor.

10.1.9.2 Study Record Retention

Study related records, including the regulatory file, study product accountability records, consent forms, participant source documents and electronic records should be maintained for a period of 2 years following the date a marketing application is approved for the investigational product for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified. These documents should be retained for a longer period, however, if required by local policies or regulations. No records will be destroyed without the written consent of the IND sponsor. Consent forms with specimen retention linked to identifiable specimens will be maintained for as long as the specimens remain in identifiable format, and a minimum of three years after use of the identifiable specimens in nonexempt human participant research.

10.1.9.3 Source Records

Source data are all information in original records (and certified copies of original records) of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data should be attributable, legible, contemporaneous, original, accurate, and complete (ALCOA-C). Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH GCP E6(R2), regulatory, and institutional requirements. For this trial, the electronic medical record is considered source data. Data recorded in the eCRF derived from source documents should be consistent with the data recorded on the source documents. Interview of participants is sufficient for obtaining medical history. Solicitation of medical records from the participant's primary care provider is not required.

10.1.10 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, any process that is

noted in the protocol and refers to details in the MOP, or GCP requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. Following a deviation(s), corrective actions should be developed by the site and implemented promptly. All individual protocol deviations will be addressed in participant study records.

It is the responsibility of the principal investigator and personnel to use continuous vigilance to identify and report deviations within five working days of identification of the protocol deviation, or within five working days of the scheduled protocol-required activity. All deviations must be promptly reported to the IND sponsor per the protocol deviation reporting procedures.

Protocol deviations must be sent to the local IRB/IEC per their guidelines. The principal investigator and personnel are responsible for knowing and adhering to their IRB requirements. A completed copy of the Protocol Deviation Form must be maintained in the Regulatory File, as well as in the participant's chart if the deviation is participant specific.

10.1.11 Publication and Data Sharing Policy

Following completion of the study, results of this research will be published in a scientific journal. Data will be available immediately following publication, with no end date, with data sharing at the discretion of the IND sponsor. Publication may occur prior to completion of a final CSR for the entire trial.

10.1.12 Human Data Sharing Plan

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

10.1.13 Genomic Data Sharing Plan

Not applicable

10.1.14 Publication

Following completion of the study, the PI is expected to publish the results of this research in a scientific journal. This study will adhere to the following publication and data sharing policies and regulations. This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH-funded research. As such, the final peer-reviewed journal manuscripts will be accessible to the public on PubMed Central no later than 12 months after publication.

10.1.15 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study will follow DMID policies and procedures for all study group members to disclose all conflicts of interest.

10.2 Additional Considerations

10.2.1 Research Related Injuries

If it is determined by the PI that an injury occurred to a participant as a direct result of the tests or treatments that are done for this study, then referrals to appropriate health care facilities will be provided to the participant. Study personnel will try to reduce, control, and treat any complications from this study. Immediate medical treatment may be provided by the participating site. No financial compensation will be provided by the NIAID, NIH, or the federal government to the participant, for any injury suffered due to participation in this trial.

10.3 Abbreviations

Abbreviation	Definition
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
BMI	Body Mass Index
BP	Blood Pressure
CAPA	Corrective and Preventative Actions
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	Confidence Interval
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CSR	Clinical Study Report
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DMID	Division of Microbiology and Infectious Diseases
eCRF	Electronic Case Report Forms
ELISA	Enzyme Linked Immunosorbent Assay
ER	Emergency Room
FDA	United States Food and Drug Administration
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMFR	Geometric Mean Fold Rise
GMP	Good Manufacturing Practices
GMT	Geometric Mean Titer
HBV	Hepatitis B
HCG	Human Chorionic Gonadotropin
HCV	Hepatitis C
HDCV	Human Diploid Cell Vaccine
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent or Institutional Ethics Committee
IM	Intramuscular
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ITT	Intention-To-Treat
LLOQ	Lower Limit of Quantification
MAAE	Medically-Attended Adverse Events
MedDRA	Medical Dictionary for Regulatory Activities

MOP	Manual of Procedures
N	Number (typically refers to participants)
NOCMC	New-Onset Chronic Medical Conditions
NHP	Nonhuman Primate
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NOCMC	New-Onset Chronic Medical Conditions
NHP	Nonhuman Primate
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NOCMC	New-Onset Chronic Medical Conditions
OHRP	Office for Human Research Protections
PBMC	Peripheral Blood Mononuclear Cell
PHI	Protected Health Information
PI	Principal Investigator
PII	Personally Identifiable Information
PIMMC	Potentially Immune-Mediated Medical Condition
QA	Quality Assurance
QC	Quality Control
RFFIT	Rapid Fluorescent Foci Inhibition Test
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SRC	Safety Review Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBILI	Total Bilirubin
UP	Unanticipated Problem
US	United States
USP	US Pharmacopeia
VAERS	Vaccine Adverse Event Reporting System
VTEU	Vaccine Treatment and Evaluation Unit
WBC	White Blood Cells
WHO	World Health Organization
TBILI	Total Bilirubin
UP	Unanticipated Problem
US	United States
USP	US Pharmacopeia
VAERS	Vaccine Adverse Event Reporting System
VTEU	Vaccine Treatment and Evaluation Unit
WBC	White Blood Cells
WHO	World Health Organization

11. PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
2.0	30 July 2024	N/A	Original version submitted to IRB
3.0	23 October 2024	Individual halting criteria added to the protocol	Administrative
		The e-Memory Aid has been removed and replaced with a paper Diary Card	Change made to address FDA concerns about the use of digital health technologies for collecting solicited AE data
		Added: "Seroconversion is defined as >4-fold rise in antibody titer...SAP."	Endpoint clarification
		Clarified that safety analysis will summarize outcomes by treatment received	Endpoint clarification
		Rabies assay normal value changed to <0.148 IU/mL	Change of rabies serology laboratory resulting in different normal cutoff
		Removed footnote and updated remaining footnote numbers	Administrative
		Updated institutional name to "University of Maryland, Baltimore"	Administrative
		Removed Objectives and Endpoints from this section; directed readers to Section 1.2	Administrative
		Removed Inclusion and Exclusion Criteria from this section; directed readers to Section 1.2	Administrative
		Added: "Study product will be administered within four hours of its preparation."	Administrative
		Extended the screening period to 60 days	To accommodate turn-around time for screening rabies serology lab test
		Procedures may be performed up to 60 days prior to enrollment	Administrative
		Expanded statement noting that study procedures, timelines, and acceptable time windows are in Section 1.2	Administrative
		Removed reference to MOP, as protocol inclusion/exclusion criteria are sufficient	Administrative
		Added: "The study will preferentially conduct an unscheduled visit in-person, but a phone visit is acceptable when necessary."	Administrative
		Clarified that SRC and ISM activities are detailed in the SRC Charter	Administrative
		Updated list of abbreviations	Better defines abbreviations used in the protocol
		Removed Section 10.4 (Protocol Amendment History)	Administrative
		Harmonized blood draw timepoints and use	Administrative
4.0	04 December 2024	Clarified in Synopsis, Section 4, Section 6.1.1, and Section 6.2.2 that Treatment Group C receives two 1400rU injections...	Administrative
		Corrected Treatment Group C antigen dose in Section 6.2.2	Administrative
		Updated Section 6.2.7 to note that vaccine administrators will be unblinded but will not participate in endpoint assessments	Administrative
		Added unblinding procedures for emergency cases in Section 6.3	Administrative
		Edited Appendix 2 blood volume table due to change in safety lab volume from 8mL to 12mL	Administrative

5.0	21 February 2025	Changed inclusion criterion #9 RFFIT threshold from <0.148 IU/mL to <0.5 IU/mL	Updated to international reference value for seroprotection
		Corrected punctuation errors in exploratory objectives	Administrative
		Changed exclusion criterion #8 rescreening window from 28 to 60 days to harmonize document	Administrative
		Edited Appendix 3 - WBC severity grading scale	Clarified FDA grading scale for WBC increase; added WBC decrease per FDA guidance
		Edited Appendix C - WBC and platelet count grading scale	Corrected values to align with reported units; previous values were off by a factor of 1000
6.0	13 June 2025	Synopsis and Section 4.1 clarified interim analysis plans, including database freeze	Administrative
		Synopsis, Section 4.1, and Section 9.4 corrected error from version 4.0 to clarify that vaccine administrators will not be blinded	Error correction
		Added Protocol Amendment History section	Administrative
		Schedule of Activities updated to include activities to be undertaken by enrolled participants who do not receive Vaccination #2	Administrative
		Throughout punctuation, formatting, and changes for sense	Administrative

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13. APPENDICES

Appendix 1. Sentinel Subgroup Halting Criteria, Individual Halting Criteria, and General Study Halting Criteria

Sentinel Subgroup Halting Criteria

Enrollment and study interventions/administration of study products will be halted for ISM review/recommendation if any of the following are reported during the 7-day observation period of sentinel subgroup participants after the first vaccination of Cohorts 1, 2, and 3:

1. Any participant experiences ulceration, abscess, or necrosis at the vaccination site that is considered related to study product administration.
2. Any participant experiences laryngospasm, bronchospasm or anaphylaxis within 24 hours after administration of study product that is considered related to study product.
3. Any participant experiences generalized urticaria (defined as occurring at more than two body parts) within 72 hours after administration of study product that is considered related to study product.
4. Any participant experiences an SAE after administration of study product that is considered related to study product.
5. Any participant experiences acute weakness of limbs and/or cranial nerve innervated muscles (description of potential signal of GBS) after administration of study product.
6. Any participant experiences a grade 3 vaccination site or systemic solicited adverse event (excluding measured grades of erythema and induration alone).

Individual Halting Criteria

The study intervention will be discontinued in an individual if:

1. The participant experiences a hypersensitivity reaction considered related to study product.
2. The participant experiences ulceration, abscess, or necrosis at the vaccination site that is considered related to study product administration.
3. The participant experiences laryngospasm, bronchospasm or anaphylaxis within 24 hours after administration of study product that is considered related to study product.
4. The participant experiences generalized urticaria (defined as occurring at more than two body parts) within 72 hours after administration of study product that is considered related to study product.
5. The participant experiences an SAE after administration of study product that is considered related to study product.
6. The participant experiences a grade 3 or greater adverse event (including laboratory tests) considered related to study product.
7. The participant becomes pregnant.
8. If the participant met an exclusion criterion for participation in the study (either newly developed or not previously recognized) that precludes further study participation.
9. The participant develops a PIMMC or AESI after administration of study product.
10. If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
11. Medical disease or condition, or new clinical finding(s) for which continued participation, in the opinion of the investigator might compromise the safety of the participant, interfere

with the participant's successful completion of this study, or interfere with the evaluation of responses.

General Study Halting Criteria

Enrollment and study interventions/administration of study products in this trial will be halted for ISM review/recommendation if any of the following are reported during the trial:

1. Any participant experiences an SAE after administration of study product that is considered related to study product.
2. Any participant experiences ulceration, abscess or necrosis at the vaccination site that is considered related to study product administration.
3. Any participant experience laryngospasm, bronchospasm, or anaphylaxis within 24 hours after administration of study product that is considered related to study product.
4. Two or more participants experience an allergic reaction such as generalized urticaria (defined as occurring at two or more body parts) after administration of vaccine that is considered related to vaccine.
5. Two or more participants experience the same Grade 3 laboratory adverse event that is considered related to study product.
6. Two (2) or more participants experience a Grade 3 AE (unsolicited) related to vaccine administration, in the same or similar Preferred Terms based on the Medical Dictionary for Regulatory Activities (MedDRA) coding.
7. Any participant experiences acute weakness of limbs and/or cranial nerve innervated muscles (description of potential signal of GBS) after administration of study product.
8. Any participant develops a PIMMC or AESI after administration of study product.
9. Two (2) participants or more experience a grade 3 vaccination site or systemic solicited adverse event.

Appendix 2. Schedule of Blood Draws and Volumes

Procedures[1]	Screening Study Visit 0 Day -60 to Day -1	Vaccination #1 Study Visit 1 Day 1	Study Visit 2 Day 3 (±1)	Study Visit 3 Day 8 (±3)	Study Visit 4 Day 22 (±7)	Vaccination #2 Study Visit 5 Day 29 (±3)	Study Visit 6 Day 31 (±3)	Study Visit 7 Day 36 (±3)	Study Visit 8 Day 61 (±3)	Study Visit 9 Day 121 (±14)	Study Visit 10 Day 210 (±14)	Study Visit 11 Day 394 (±14)	Unscheduled Visit[2]	Early Termination Visit[2]
Type of Visit	**Clinic**	**Clinic**	**Phone**	**Clinic**	**Clinic**	**Clinic**	**Phone**	**Clinic**	**Clinic**	**Clinic**	**Phone**	**Clinic**	**Clinic**	**Clinic**
Clinical														
• Hematology/Chemistries	8			12				12	12				12	12
• HIV, HCV, HbsAg, Serum Pregnancy Test	4													
• Rabies neutralization	4													
Total clinical blood volume (scheduled)	16			12				12	12				12	12
Immunology														
• IgG ELISA		15		15		15		15	15	15		15	15	15
• PBMC		80		50		50		50	50	50		50	50	50
Total immunology blood volume		95		65		65		65	65	65		65	65	65
Total visit volume	16	95	N/A	77	N/A	65	N/A	77	77	65	N/A	65	77	77
Cumulative volume[3]	16	111	111	188	188	253	253	330	407	472	472	537		

1. Volumes are in milliliters (mL), are approximate, and may be adjusted to meet the clinical site's requirements.
2. Blood draws at the investigator discretion.
3. Total scheduled blood volume is approximately 537mL per participant over the 13-month trial participation.

Appendix 3: Grading Scale for Clinical Laboratory Values

	Grade for Abnormal Results			
Parameter	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Creatinine (mg/dL)	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Total bilirubin (mg/dL)	1.1 – 1.5 x ULN* 1.1 – 1.25 x ULN**	1.6 – 2.0 x ULN* 1.26 – 1.5 x ULN**	2.0 – 3.0 x ULN* 1.51 – 1.75 x ULN**	> 3.0 x ULN* > 1.75 x ULN**
ALT (SGPT) (U/L)	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
WBC Increase- (K/µL, K/mm^3 or 10^9/L)	10.800 – 15.000	15.001 – 20.000	20.001 – 25. 000	> 25.000
WBC Decrease- (K/µL, K/mm^3 or 10^9/L)	2.500 – 3.500	1.500 – 2.499	1.000 – 1.499	< 1.000
Hemoglobin (g/dL)	M: 12.5 – 13.5 F: 11.0 – 12.0	M: 10.5 – 12.4 F: 9.5 – 10.9	M: 8.5 – 10.4 F: 8.0 – 9.4	M: < 8.5 F: < 8.0
Platelet count (K/µL, K/mm^3 or 10^9/L)	125.000 – 140.000	100.000 – 124.000	25.000 – 99.000	< 25.000

Note: ULN=upper limit of normal; LLN=lower limit of normal.

[1] FDA Guidance for Industry Toxicity Grading Scale for Healthy Adults Enrolled in Preventive Vaccine Clinical Trials, 2007.

* Tox grading for total bilirubin when liver transaminases are normal.

** Tox grading for total bilirubin when accompanied by increased transaminases.

Appendix 4: Grading Scale for Local Injection Site Reactions

Local Reaction to Injectable Product	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Potentially Life Threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of nonnarcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness*	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling **	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

Note: Local injection site reaction grading should not be confused with general AE grading.
* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.
** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Appendix 5: Grading Scale for Determining the Severity of Abnormal Vital Signs

Vital Signs*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever: oral (˚C)** (˚F)**	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia – bpm	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia*** – bpm	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) mm Hg	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate– breaths per minute	17 – 20	21 – 25	> 25	Intubation

* Participants should be at rest for at least 5 minutes prior to vital sign measurements
** Oral temperature; no recent hot or cold beverages or smoking. Note: A fever can be considered not related to the study product if an alternative etiology can be documented and it is confirmed to be not related to the study product by the Independent Safety Monitor at the site.
*** When resting heart rate is between 60-100 beats per minute. Use clinical judgment when characterizing bradycardia among some healthy participant populations, for example conditioned athletes.

Appendix 6: Grading Scale for Determining the Severity of Clinical AEs

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Headache	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	Does not interfere with activity	Interferes with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia (generalized muscle pain)	Does not interfere with activity	Interferes with activity	Significant; prevents daily activity	ER visit or hospitalization
Arthralgia (joint pain)	Does not interfere with activity	Interferes with activity	Prevents daily activity	ER visit or hospitalization
Chills	Does not interfere with activity	Interferes with activity	Prevents daily activity	ER visit or hospitalization
Anorexia (loss of appetite)	Does not interfere with activity	Interferes with activity	Prevents daily activity	ER visit or hospitalization
Nausea/Vomiting	Does not interfere with activity or 1 – 2 episode in 24 hours	Interferes with activity or >2 episodes in 24 hours	Prevents daily activity or requires outpatient IV hydration	ER visit or hospitalization
Diarrhea	2-3 loose stools or < 400 grams/24 h	4-5 stools or 400-800 grams/24 hours	6 or more watery stools or >800 grams/24 hours or requires outpatient IV hydration	ER visit or hospitalization

Appendix 7: List of PIMMCs

This list is provided by U.S. FDA/CBER and is participant to periodic update. Any updates will be implemented via a Note to File. The investigator should exercise their clinical judgement as to whether other diseases or conditions that do not appear on this list are autoimmune or autoinflammatory in nature and should be reported as a PIMMC.

<table>
<tr><th>Gastrointestinal disorders</th><th>Liver disorders</th><th>Metabolic diseases</th></tr>
<tr><td>• Celiac disease
• Crohn’s disease
• Ulcerative colitis
• Ulcerative proctitis</td><td>• Autoimmune cholangitis
• Autoimmune hepatitis
• Primary biliary cirrhosis
• Primary sclerosing cholangitis</td><td>• Addison’s disease
• Autoimmune thyroiditis (including Hashimoto thyroiditis)
• Diabetes mellitus type I
• Grave’s or Basedow’s disease</td></tr>
<tr><th>Neuroinflammatory disorders</th><th>Musculoskeletal disorders</th><th>Skin disorders</th></tr>
<tr><td>• Acute disseminated encephalomyelitis, including site specific variants (e.g., non-infectious encephalitis, encephalomyelitis, myelitis, radiculomyelitis)
• Cranial nerve disorders, included paralyses/paresis (e.g., Bell’s palsy)
• Guillain-Barré syndrome, including Miller Fisher syndrome and other variants
• Immune-mediated peripheral neuropathies and plexopathies, including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy
• Multiple sclerosis
• Myasthenia gravis, including Eaton-Lambert syndrome
• Narcolepsy
• Optic neuritis
• Transverse myelitis</td><td>• Antisynthetase syndrome
• Dermatomyositis
• Juvenile chronic arthritis (including Still’s disease)
• Mixed connective tissue disorder
• Polymyalgia rheumatic
• Polymyositis
• Psoriatic arthropathy
• Relapsing polychondritis
• Rheumatoid arthritis
• Scleroderma, including diffuse systemic form and CREST syndrome
• Spondyloarthritis, including ankylosing spondylitis, reactive arthritis (Reiter’s Syndrome) and undifferentiated spondyloarthritis
• Systemic lupus erythematosus
• Systemic sclerosis</td><td>• Alopecia areata
• Autoimmune bullous skin diseases, including pemphigus, pemphigoid and dermatitis herpetiformis
• Cutaneous lupus erythematosus
• Erythema nodosum
• Morphoea
• Lichen planus
• Psoriasis
• Rosacea
• Sweet’s syndrome
• Vitiligo</td></tr>
<tr><th>Vasculitides</th><th colspan="2">Others</th></tr>
<tr><td>• Large vessels vasculitis including: giant cell arteritis such as Takayasu’s arteritis and temporal arteritis
• Medium sized and/or small vessels vasculitis including: polyarteritis nodosa, Kawasaki’s disease, microscopic polyangiitis, Wegener’s granulomatosis, Churg-Strauss syndrome (allergic granulomatous angiitis), Buerger’s disease thromboangiitis obliterans, necrotizing vasculitis and anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified), Henoch-Schonlein purpura, Behcet’s syndrome, leukocytoclastic vasculitis</td><td colspan="2">• Antiphospholipid syndrome
• Autoimmune hemolytic anemia
• Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis)
• Autoimmune myocarditis/cardiomyopathy
• Autoimmune thrombocytopenia
• Goodpasture syndrome
• Idiopathic pulmonary fibrosis
• Pernicious anemia
• Raynaud’s phenomenon
• Sarcoidosis
• Sjögren’s syndrome
• Stevens-Johnson syndrome
• Uveitis</td></tr>
</table>