Statistical Analysis Plan

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

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Study Title:	**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**
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LIST OF ABBREVIATIONS

℃	degrees Celsius or Centigrade
≤	less than or equal to
µg	microgram
µL	microliter
µm	micrometer
AE	Adverse Event/Adverse Experience
AESI	Adverse Event of Special Interest
APHAD	3D-(6-Acyl) monophosphoryl Hexa-acyl Lipid A, 3-deacyl
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
DMID	Division of Microbiology and Infectious Diseases, NIAID, NIH, DHHS
ELISA	enzyme-linked immunosorbent assay
FDA	Food and Drug Administration
g	gram(s)
GMFR	Geometric mean fold rise
GMT	geometric mean titer
HDCV	Human diploid cell vaccine (commercially available rabies vaccine)
HIPAA	Health Insurance Portability and Accountability Act
IgG	immunoglobulin g
IND	Investigational New Drug application
IRB	Institutional Review Board
IU	International Unit
LASSARAB	Rabies-Vectored Monovalent Lassa Fever Vaccine
LASV-GPC	Lassa virus glycoprotein complex
L	liter
LLOQ	Lower limit of quantitation
MAAE	medically attended adverse events
MedDRA	Medical Dictionary for Regulatory Activities
mL	milliliter(s)
N	Number (typically refers to subjects)
NOCMC	new onset chronic medical condition
PI	Principal Investigator
PIMMC	potentially immune-mediated medical condition

RABV-G	Rabies virus glycoprotein
RFFIT	Rapid Fluorescent Foci Inhibition Test
SAE	Serious Adverse Event/Serious Adverse Experience
SE	Stable oil-in-water emulsion
SRC	Safety Review Committee
SNHL	New onset sensorineural hearing loss
WHO	World Health Organization

1 INTRODUCTION

This Statistical Analysis Plan (SAP) for DMID Protocol 23-0015, "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," describes and expands upon the statistical information presented in the protocol.

The purpose of this Statistical Analysis Plan (SAP) is to ensure that the summary tables, figures and listings (TLFs) which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives. Individual study results, appropriate summary statistics for study conduct (including subject disposition and demographics), and safety assessments will be presented.

The SAP is organized as follows: Sections 4 will review the study design, Sections 5 will cover general statistical considerations and methods, including subject disposition, Sections 6 will discuss the general statistical methodology, including reporting conventions, and Section 7 will discuss in detail the general statistical analyses. The Appendices are comprised of Appendix I: Tables and Appendix II: Listings. Deviations from this SAP will be discussed and justified in the final CSR.

2 CHANGES FROM PROTOCOL IN STUDY CONDUCT OR ANALYSIS

There are no changes from the protocol in the study conduct or analysis, but some clarification of terms used in the protocol is necessary. The protocol states that the primary analysis population for safety evaluations will be all subjects having received at least an initial dose of study treatment. It defines this population as the "Intent-To-Treat (ITT) population." For immunology analyses, the protocol describes the analysis population as the "Modified Intention-To-Treat (mITT) population." In summary, this population includes all participants having received at least an initial dose of study treatment and for whom data are available at a particular endpoint date.

3 STUDY OBJECTIVES AND ENDPOINT MEASURES

The purpose of the study is to inform selection of the optimal dose level(s) for further study. This purpose applies to all primary and secondary objectives. See Table 1 and Table 2 for schedules of study procedures by treatment group.

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 LASV GPC by enzyme linked immunosorbent assay (ELISA) at Day 1, 8, 29, 36, and 61 per treatment group • Percentage of participants seroconverting for Lassa virus GPC IgG at Day 8, 29, 36, and 61 per treatment group (where seroconversion is defined as $\geq$ 4-fold rise in antibody titer at any time point as compared to Day 1.)
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. • Percentage of participants seroconverting for rabies antibodies at Day 8, 29, 36, and 61 per treatment group where seroconversion is defined as a rise in rabies neutralizing antibody test from <0.5 IU/mL at day 1 to ≥ 0.5 IU/mL at any subsequent timepoint • 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 virus IgG 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 Day 1.)

Additional protocol-specified exploratory objectives and endpoints are detailed in the protocol.

3.1 Study Definitions and Derived Variables

3.1.1 Safety Variables

Safety parameters to be evaluated after vaccination and assessed in terms of the incidence of include:

- Solicited Systemic reactogenicity: headache, nausea, tiredness, joint pain, body aches/ muscular pain, feverishness, feel like having hearing loss
- Solicited Local reactogenicity: warmth, tenderness, itching, pain, redness (with measurement), swelling (with measurement)
- Unsolicited adverse events
- Medically attended adverse events (MAAEs)
- New onset chronic medical conditions (NOCMCs)
- Potentially immune-mediated medical conditions (PIMMCs)
- Serious adverse events (SAEs)
- Adverse Event of Special Interest (AESI), new onset sensorineural hearing loss (SNHL)
- Clinical laboratory adverse events. Parameters to be evaluated include white blood cells, hemoglobin, platelets, alanine transaminase, creatine, and total bilirubin.

3.1.2 Immunogenicity Variables

Lassa antibody (IgG) response will be measured using ELISA (LASV-GPC) in serum samples obtained prior to vaccination on days 1 and 29, and at days 8, 36, 61, 121 and 394. The lower limit of quantitation (LLOQ) for the LASV-GPC IgG assay is 0.69 IU/mL. For samples with Ab concentrations < 0.69 IU/mL, the titer will be reported as 0.35 IU/mL. Seroconversion is defined as either ≥ four-fold rise from pre-vaccination titer to post-vaccination antibody titer or as an increase in serum IgG titer from below LLOQ to 2.76 IU/ml or greater post-vaccination.

Rabies antibody response will be measured using RFFIT test (Rapid Fluorescent Foci Inhibition Test) assessed from venous blood taken prior to vaccination on days 1 and 29, and at days 8, 36, 61, 121 and 394. For rabies virus RFFIT assay, seroprotection is defined as rabies neutralizing antibody titer ≥ 0.5 IU/mL at any timepoint. Seroconversion is defined as a rise in rabies neutralizing antibody titer from <0.5 IU/mL at day 1 to ≥ 0.5 IU/mL at any subsequent timepoint.

Rabies antibody (IgG) response will be measured using ELISA (RABV-G) in serum samples obtained prior to vaccination on days 1 and 29, and at days 8, 36, 61, 121 and 394. The LLOQ for the Rabies IgG ELISA is 0.004071 IU/mL (4.07 mIU/ml). For samples with Ab concentrations < 4.07 mIU/mL, the titer will be reported as 2.035 mIU/mL. Seroconversion is defined as either ≥ four-fold rise from pre-vaccination titer to post-vaccination antibody titer or as an increase in serum IgG titer from below LLOQ to 16.28 mIU/ml or greater post-vaccination.

For each assay, the following will be calculated: 1) Geometric Mean Titers; 2) Geometric Mean Fold Rise (fold rise will be calculated as the ratio of post-vaccination titer/ pre-vaccination titer, where pre-vaccination value

is always the result obtained at day 1 prior to any study vaccination; 3) Percent Seroconversion (participants achieving ≥ 4-fold rise in ELISA antibody titer at any time point as compared to day 1 or rise in RFFIT neutralizing antibody titers from <0.5 IU/mL at day 1 to ≥ 0.5 IU/mL at any subsequent timepoint). For RFFIT, percent seroprotection (participants achieving rabies neutralizing antibody titer ≥ 0.5 IU/mL at any timepoint) will be calculated.

4 TRIAL DESIGN

4.1 Design Overview

Refer to the study protocol Synopsis Section 1.1 and Section 4 for details of trial design.

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.

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 2800 rU 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.

4.2 Study Population and Eligibility Criteria

This study will enroll up to 55 generally healthy males and non-pregnant females aged 18 through 50 years, inclusive, 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, as provided in the protocol Section 1.2 and Section 5.

4.3 Replacement of Subjects Withdrawn from Study

Subjects will not be replaced if they are withdrawn from the study.

4.4 Randomization and Allocation Procedures

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.

4.5 Study Duration

Within 60 days of screening (Visit 0), subjects that are enrolled will receive the first vaccination and will be followed for 394 days (approximately 1 year after receipt of the second vaccination).

4.6 Sample Size Considerations

This study is not designed to test a formal null hypothesis. The sample size is chosen without the intention that group differences will be detected with sufficient power but is consistent with FDA guidance. It is intended to obtain sufficient data to obtain meaningful estimates of the immune response and to uncover any safety issues that occur at a sufficiently high rate that they might be observed in a study of this size. Among the 55 participants, 15 people will be randomized to each of three dose groups (Treatment Groups A, B, and C) for LASSARAB+aPHAD-SE and 10 persons to the HDCV control group (Treatment Group D).

5 GENERAL STATISTICAL CONSIDERATIONS AND METHODS

5.1 Analysis Populations

The primary analysis population will be all subjects having received at least an initial dose of study treatment. This is defined as the Safety Analysis Set for safety evaluations. For immunology analyses, the analysis population will be all subjects having received at least an initial dose of study treatment and for whom data are available at a particular endpoint date. This is defined as the Modified Intention-to-Treat Analysis Set. Data displays produced for this study will include two types—summary tables and data listings. Figures, such as scatter dot plots, will be produced to visually display individual participant responses to Lassa and Rabies antigens.

5.2 Subject Disposition

A summary of subject disposition will summarize, overall and by treatment group, the numbers and percentages of subjects who were consented and screened, enrolled, completed each visit, and completed the study. The percentages will be based on the number of enrolled subjects. The reasons that subjects were screened but not enrolled will be summarized. Subjects prematurely withdrawn, by subject or physician decision, discontinued from the study or lost to follow up will be listed and each of the reasons defined in the protocol.

5.2.1 Measurements of Treatment Compliance

All subjects are to receive two doses of vaccine administered 28 days apart. The number of study vaccinations administered to subjects will be presented by treatment group. A listing of subjects who received investigational product with randomized treatment group and study product received for each vaccination will be presented.

5.3 Protocol Deviations

Any protocol deviation that adversely affects the safety or rights of a subject or the scientific integrity of the study will be reported immediately to the sponsor's representative and the IRB, in the manner described in the study protocol. A summary of subject-specific and non-subject-specific protocol deviations will be presented by the deviation category and deviation type, and treatment group for all enrolled subjects.

5.4 Subject Characteristics

Characteristics of subjects will be summarized or listed as described below.

5.4.1 Demographics:

The following will be summarized for all enrolled subjects: age, sex, ethnicity, race, and BMI, by treatment group. **Age will be summarized as a continuous variable**. Age will be calculated as the number of years elapsed between birth date and the date of informed consent, adjusted for whether the birthday has passed

as of the day of signing. **Ethnicity is categorized as Hispanic or Latino, or not Hispanic and not Latino.** BMI will be summarized as continuous. A listing of demographics will also be presented.

5.4.2 Baseline Medical History:

Medical history is collected at the screening visit. A listing for subjects medical history will be presented for the Safety Analysis population.

5.4.3 Prior and Concurrent Illnesses and Medical Conditions

All current illnesses and past or pre-existing medical conditions will be coded using Medical Dictionary for Regulatory Activities (MedDRA). Summaries of subjects' prior and concurrent medical conditions will be presented by treatment group. Individual subject listings will be presented for all reported medical history including prior and concurrent medical conditions.

5.4.4 Prior and Concurrent Medications

All medications and vaccines taken within 60 days prior to screening and until study Day 61 will be documented. Concomitant medications will be coded to the Anatomical Therapeutic Classification using the WHO Drug Dictionary. A listing of concomitant medications, ordered within subject by the Start Date will be documented, displaying the recorded term from the CRF and, adjacent to that, the WHO Drug preferred term and medication name and therapeutic indication. The use of concomitant medications during the study will be summarized by treatment group for the Safety population.

5.4.5 Physical Examination

Physical examination findings associated with adverse events will be incorporated into adverse event reports and summarized in the relevant AE tables/listings. Targeted physical examinations will be performed, if indicated, based on a subject's medical history.

5.4.6 Vital Signs

Abnormal vital signs determined to be adverse events will be reported as adverse events and summarized in the relevant AE tables/listings. Vital signs oral temperature, systolic blood pressure, diastolic blood pressure, and pulse will be assessed at every in-person visit. The vital signs will be graded per the FDA Guidance for Industry Toxicity Grading Scale for Healthy Adults Enrolled in Preventive Vaccine Clinical Trials, 2007.

5.4.7 Pregnancies

For any subjects in the Safety population who became pregnant during the study, every attempt will be made to follow these subjects to completion of pregnancy to document the outcome, including information regarding any complications with pregnancy and/or delivery. All study pregnancies and their outcomes will be tabulated.

6 GENERAL STATISTICAL METHODOLOGY

6.1 Data Sources

CRF data are extracted from the clinical database.

6.2 Missing Data

Missing data will be handled according to Table 3. All attempts will be made to collect all data per protocol. As missing data are expected to be minimal, no imputation will be performed for missing values. Any data point that appears to be erroneous or inexplicable based on clinical judgment will be investigated as a possible outlier. If data points are identified as outliers, sensitivity analyses will be performed to examine the impact of including or excluding the outliers. Any substantive differences in these analyses will be reported.

Table 3 Methods for Handling Missing Data and Outliers

Data	Handling Method
Safety	Missing data will not be replaced with imputed values.
Causality	Non-serious unsolicited AEs and SAEs with missing causality will be considered as related to inoculation.
Measurements	Missing measurement (for temperature) will not be replaced. Nevertheless, the following rule will be applied: If temperature is partially missing after decimal point, the data will be analyzed replacing "MD" by zero (whatever the group). By example, a "39.MD" daily temperature (MD means missing data) will be considered as "39.0°C" at the time of analysis.
Intensity	Missing intensity will not be imputed.
Start and Stop Dates	Missing or partially missing stop dates will not be imputed. If the exact date not known, then the month and year will be recorded.
Action Taken	Missing action taken will not be imputed.
Assessment of Outcome	Assessment of outcome will not be imputed.
Seriousness (for SAE)	Missing seriousness will not be imputed. Missing seriousness will be indicated as such in the data listings.

6.3 Baseline Assessments

Results of baseline assessments of demographics and immunogenicity will be summarized. Hypothesis tests will not be used for comparison of pretreatment data among cohorts. Clinical judgment of the importance of any differences among treatment groups will be addressed in the study report.

6.4 Definition of Baseline and Change from Baseline

When analysis requires identification of a baseline value, the last value prior to the first administration of a study vaccine will be used.

6.5 Covariates and Subgroups

No adjustment will be made for effects of covariates and subgroups.

6.6 Sample Size Reassessment

No sample size reassessment was planned for this study.

6.7 Test Size

Hypotheses will not be tested as part of the analysis of study data, and so test sizes are not relevant to this study

6.8 Multiple Testing/Multiple Comparisons/Multiplicity

Since hypotheses will not be tested as part of the analysis of study data, control of the effect of multiple comparisons is not relevant to this study. This study was designed to obtain preliminary estimates of safety and immune response to LASSARAB+aPHAD-SE vaccination in healthy adults. The study was not designed to test any specific null hypothesis, and as such, the type one error rate, alpha = 0.05, is not adjusted for multiple comparisons.

6.9 Data Display Characteristics

Summary tables will be produced as specified in the following statistical analyses sections. Summary tables will display summary statistics calculated for each of the study treatment arms (if applicable), unless described otherwise in the following statistical analyses sections.

Data listings will list the data recorded in the clinical database or derived for each subject. They will be ordered by study treatment arm, subject number, and date/time of assessment. Data listings will also display Study Day, where applicable. For example, the first vaccination day is displayed as Day 1, study procedures occurring before Day 1 will be reported as occurring during the screening period (Days -60 to -1). When expedient, additional levels of ordering hierarchy may reflect subsets of assessments within subjects. Data listings will not display subject initials or any unique identifiers that violate HIPAA.

Unless stated otherwise in relevant sections to follow, continuous data will be summarized with the number of non-missing values, mean, standard deviation, median, minimum, and maximum. Unless stated otherwise, categorical data will be summarized with the number of non-missing values and the numbers of values equal to each of the possible categories. Unless stated otherwise, percentages of subjects with each of the possible values will be calculated using the number of subjects with non-missing data for endpoints where results are expected to be obtained including lab tests and solicited data. For AEs, since these are spontaneous reports collected by date of onset, the number of subjects in the corresponding analysis population will be used as the denominator.

6.10 Reporting Conventions

P-values ≥0.001 and ≤0.999 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001"; p-values greater than 0.999 will be reported as "> 0.999". The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the

original data. Proportions will be presented as two decimal places; values <0.01 will be presented as "<0.01". Percentages will be reported to the nearest whole number; non-zero values < 1% will be presented as "<1"; values greater than 99% but less than 100% will be presented as >99.

7 GENERAL STATISTICAL ANALYSES

The analyses will be performed under the responsibility of Dr. Yuanyuan Liang of the University of Maryland, Baltimore. Analysis of the data from this study will be descriptive in nature. Confidence intervals and p-values will not be generated as part of the final summaries for safety and reactogenicity due to the small sample size of this study, unless otherwise specified in subsequent sections. Mean, standard deviation, and possibly median and quartiles will be used for continuous data and number and percentage will be used for categorical data, unless specified otherwise.

7.1 Analysis Summary

In general, all data will be listed, sorted by treatment and subject, and when appropriate by visit number within subject. All summary tables will be structured with a column for each treatment group. All tables will be annotated with the total population size relevant to that table/treatment, including any missing observations. All subjects receiving at least one dose of study treatment will be included in the analysis. Descriptive summary statistics will be provided for all assays at each time point. There will be a final statistical analysis conducted following the end of all study visits.

Summary tables and line listings will be presented for safety and immunogenicity data. Adverse Events (AEs) will be tabulated for each treatment arm. Serious Adverse Events (SAEs) will be summarized separately. The frequency and severity of systemic and local solicited AEs will be tallied for each treatment group. All AEs and laboratory AEs will be presented by subject listings.

Geometric mean titer and corresponding 95% confidence intervals will be calculated for each group. For binary outcomes such as seroconversion (Yes/No), proportion will be calculated for each group with the corresponding 95% confidence intervals using Clopper Pearson exact method. At each time point of interest, the difference in proportions between the treatment arms will be compared using Fisher's exact test or Chi-square test as appropriate.

For continuous outcomes, such as BMI and age, mean, standard deviation, median and interquartile range will be calculated for each group. At each time point, the difference in continuous outcomes of interest between the treatment groups will be compared using Kruskal-Wallis H-test or ANOVA F-test on the log-transformed (base 10) scale as appropriate. Pairwise comparison will be conducted if needed. Wilcoxon signed-rank test will be used to compare differences in antibody titers across time points within each vaccine group. All analyses will be performed using Stata/SE version 18.0 (Stata Corp, College Station, TX) or SAS, version 9.4 (Copyright ® 2016 SAS Institute Inc).

7.2 Sentinel Subject Safety Review

Regular or ad hoc sentinel subject safety reviews will occur during the trial by a Safety Review Committee (SRC). They are described in detail in the protocol in Section 10.1.6.

There are no statistical criteria for study termination in this clinical trial. Raw data on safety will be extracted from the database system and presented to the study SRC for recommendation of appropriate follow-up options per the SRC charter. No formal statistical analysis will be performed for SRC reviews.

7.3 Interim Analysis

An interim analysis of available safety and immunogenicity data will be conducted while the study is ongoing. This 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. This database freeze will include fields from the following instruments: Demographics, Vital Signs, Inclusion/Exclusion Criteria, Vaccine Administration, Reactogenicity Assessment, Laboratory Results and Adverse Events. After the 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, who will be unblinded, including summaries of clinical safety and secondary immunogenicity data by study group. To maintain blinding of principal investigator, sponsor and blinded study staff, results will be presented in summary tables by vaccine 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 published. The interim analysis will include the following tables listed in Appendix 1: Enrollment and Compliance (Table 5), Demographic and Baseline Characteristics (Table 6), serum LASSA GPC IgG ELISA (Table 7, through Day 61), serum rabies GP IgG RFFIT and ELISA (Table 8, through Day 61), Overall Summary of Adverse Events (Table 9), Local and Systemic Solicited Events after first vaccination (Tables 10-11, 14-15) and second vaccination (Tables 12-13, 16-17), Summary of Unsolicited Adverse Events and Laboratory Abnormalities (Table 19, through Day 61), and listings of Unsolicited Adverse Events (Listing 11) and Clinical Laboratory Adverse Events (Listing 13) by treatment group.

A study biostatistician will have access to unblinded, individual level data, will complete analyses, and will make results available as aggregated, summary data by study arm and timepoint to the study team, sponsor, funding agency, and vaccine developer. Investigators (with the exception of biostatisticians and designated unblinded study personnel participating in vaccine administration) will remain blinded at this stage and will only be unblinded after study completion and final dataset lock. Line listings containing individual level data will be included in the final CSR when all investigators are unblinded.

7.4 Statistical Analysis for Primary Objectives

There are no hypotheses. All of the main analyses will be descriptive by treatment group. The safety analysis set will be used for the analysis of safety data in this study.

7.4.1 Severity Assessment

All adverse events (AEs) will be assessed for severity by the investigator. Inherent in this assessment is the medical and clinical consideration of all information surrounding the event including any medical intervention required. Each event will be graded using the following scales found in the study protocol:

- For solicited adverse events and laboratory testing abnormalities, grading will be according to the FDA Guidance for Industry Toxicity Grading Scale for Healthy Adults Enrolled in Preventive Vaccine Clinical Trials, 2007

- For adverse events not included in the FDA Guidance for Industry scale, severity will be assessed per the protocol Section 8.4.3.1 and relationship to study intervention per protocol Section 8.4.3.2.

The maximum intensity of laboratory test abnormalities, solicited and unsolicited AEs will be determined by the highest severity recorded if an occurrence happens more than once. If an AE or laboratory test abnormality is non-continuous (i.e., occurring over two separate periods with at least one intervening day), the maximum intensity will be the highest severity observed across both periods.

7.4.2 Solicited AEs

A solicited AE is a predetermined event. Systemic and local solicited adverse events will be collected within 30 minutes post-vaccination, and daily for 7 days after each vaccination.
Individual solicited local and systematic AEs immediately following vaccination and over the 7-day follow-up period will be analyzed using the safety dataset. The incidence of individual solicited AEs will be calculated overall, by treatment group, type of reactions, duration and maximum severity in summary tables. Individual subject listings will also be provided. Presentations will include the number and percentage of subjects with at least one solicited symptom (local or systemic), at least one local symptom, and at least one general (systemic) symptom, as well as the incidence of each symptom individually. When calculating the incidence of solicited events, each subject will be counted once at the highest severity following the applicable vaccination, and any repetitions will be ignored.

For summaries presented separately for each vaccination, the denominator for percentages will be the number of subjects who received the respective vaccination with non-missing data for the event summarized. For summaries over all vaccinations the denominator will be the number of subjects who received at least one vaccination with non-missing data for the event summarized.

7.4.3 Unsolicited AEs

Unsolicited adverse events are any other AEs that occur following administration of study product. This will be collected via discussions between the PI, study staff and subject at each clinic visit and observations by the Investigator. The number of subjects with at least one report of an unsolicited adverse event reported up to 28 days after each vaccination will be summarized overall and by treatment group. The intensity and temporal relationship of the unsolicited symptoms to immunization will also be assessed. Presentations will also summarize unsolicited AEs by MedDRA coding using preferred term, organ body system, grade, and relatedness to vaccination. Any events in the database with onset not within any of the periods described above will not be summarized but will be included in subject AE listing.

For the tabulation of the unsolicited AEs by MedDRA system organ class and preferred term, a subject will be counted only once in a given body system. For example, a subject reporting nausea and diarrhea will be reported as one subject, but the symptoms will be listed as two separate unsolicited AEs within the class. Therefore, the total number of TEAEs reported within a body system may exceed the number of subjects within the body system reporting unsolicited AEs.

For summaries by severity, if a subject has more than one event within the same preferred term, the most severe event episode will be counted.

For summaries of vaccine-related unsolicited AEs, if a subject has more than one event within the same preferred term, and if one event is considered "not related" and the other "related", the subject will be counted as "related" for that term.

Data Listings will present the verbatim-reported event along with the Preferred Term (PT) and System Organ Class (SOC), duration, severity, relatedness, SAE status, action taken, and outcome.

7.4.4 Deaths, Serious Adverse Events and other Significant Adverse Events

The following listings will be presented including Subject ID, Age (years), AE Description, AE Onset Date/End Date, Last Vaccination Received/Days Post Vaccination, Reason Reported as an SAE, Relationship to Treatment, Alternate Etiology if not Related, Outcome, and Duration of Event (days):

- Serious Adverse Events (SAEs)
- Medically-Attended Adverse Events (MAAEs)
- Potential Immune-Mediated Medical Conditions (PIMMCs)
- New-Onset Chronic Medical Conditions NOCMCs
- AESI Adverse Event of Special Interest

7.4.5 Laboratory Test Abnormalities

Clinical laboratory evaluations (blood draw for safety labs) consist of serum chemistry and hematology assessments as specified in the protocol. Clinical safety laboratory parameters (white blood cell count, platelet count, hemoglobin, creatinine, alanine aminotransferase (ALT), total bilirubin) will be collected from each subject prior to each study vaccination for baseline and then 7 days after vaccination for doses 1 and 2.

Clinical laboratory AEs are defined as laboratory abnormalities with a grade level increase in clinical laboratory values per protocol toxicity tables. If the lab abnormality results in the diagnosis of a new medical condition, that condition should be captured as an AE. Abnormal laboratory measurements that occur following each vaccination over a 28-day follow-up period will be summarized overall, by treatment group, by duration and by toxicity grade for each study vaccination. A summary of subjects with shifts from baseline (relative to normal range) in laboratory test results will be provided.

7.5 Statistical Analysis for Secondary and Exploratory Objectives

There are no hypotheses. All of the main analyses will be descriptive by treatment group.

Immunogenicity data summaries and analysis for immunologic endpoints will be presented for the mITT populations as described in the protocol and above in Section 2l. Immune responses will be summarized by treatment group at each time point. Descriptive summary statistics will be provided for all assays and time points including number of subjects with non-missing results, percentage of subjects achieving seroprotection, where applicable, seroconversion, and GMTs along with corresponding 95% CI. Exact confidence intervals will be presented for proportional endpoints.

7.5.1 Lassa Humoral Immune Response

Serum IgG antibody concentrations, expressed in ELISA Units per mL (EU/mL), specific for Lassa virus glycoprotein complex (LASV-GPC) will be measured by ELISA. For analysis, the geometric mean for each timepoint will be computed and used as the response for all subsequent calculations. The

secondary immunogenicity endpoints antibody titer seroconversion and geometric mean fold rise will be summarized using Day 8, 29, 36, 61, 121 and 394 values compared to baseline value (Day 1).

7.5.2 Rabies Primary ELISA Response

Serum IgG antibody concentrations, expressed in ELISA Units per mL (EU/mL), specific for rabies virus glycoprotein (RABV-G) will be measured by ELISA. For analysis, the geometric mean for each timepoint will be computed and used as the response for all subsequent calculations. The secondary immunogenicity endpoints Ab titer seroconversion and geometric mean fold rise will be summarized for Day 8, 29, 36, 61, 121, and 394 compared to baseline value (Day 1).

7.5.3 Rabies Primary RFFIT Response

The virus-neutralizing antibodies will be determined using the Rapid Fluorescent-Focus Inhibition Test (RFFIT). The World Health Organization (WHO) standard of rabies IgG is used as a standard and international units (IU)/mL over 0.5 IU are considered positive.

APPENDIX I: TABLES

Table 4 Ineligibility Summary of Screen Failures

Inclusion/Exclusion Category	Inclusion/Exclusion Criterion	n	%
Inclusion and Exclusion	Number of subjects failing any eligibility criterion	x	x
Inclusion	Any inclusion criterion	x	x
	[inclusion criterion 1]	x	x
	[inclusion criterion 2]	x	x
	[inclusion criterion 3]	x	x
Exclusion	Any exclusion criterion	x	x
	[exclusion criterion 1]	x	x
	[exclusion criterion 2]	x	x
	[exclusion criterion 3]	x	x

Table 5 Enrollment and Compliance

	Group A Number (%)	Group B Number (%)	Group C Number (%)	Group D Number (%)	Overall Number (%)
Visit 0: Consented and Screened					
Screen Fails*					
Eligible but not Enrolled					
Visit 1: Enrolled and Vaccinated (Dose #1)					
Visit 2: Completing Day 3 Phone Call					
Visit 3: Completing Day 8 Visit					
Visit 4: Completing Day 4 Visit					
Visit 5: Vaccinated (Dose #2)					
Visit 6: Completing Day 31 Phone Call					
Visit 7: Completing Day 36 Visit					
Visit 8: Completing Day 61 Visit					
Visit 9: Completing Day 121 Visit					
Visit 10: Completing Day 210 Phone Call					
Visit 11: Completing Day 394 Visit					
Protocol Completed					

*Reason for screen fails

Table 6 Summary of Categorical Demographic and Baseline Characteristics by Treatment Group, All Enrolled Subjects

	Group A Number (%)	Group B Number (%)	Group C Number (%)	Group D Number (%)	Overall Number (%)
Age					
Mean					
Standard Deviation					
Median					
Minimum					
Maximum					
BMI					
Mean					
Standard Deviation					
Median					
Minimum					
Maximum					
Sex					
Female					
Male					
Other					
Ethnicity					
Hispanic					
non-Hispanic					
Other					
Race					
American Indian or Alaskan Native					
Asian					
Native Hawaiian or other Pacific Islander					
Black or African American					
White					
Other					
Unknown					

Table 7 Summaries of Serum LASSA GPC IgG ELISA by Study Day and Treatment Group

Time Point	Group A	Group B	Group C	Group D
Baseline (Pre-Dose 1) (Day1)				
n				
GMT (95%CI)				
Day8				
n				
GMT (95%CI)				
Seroconversion % (95%CI)				
GMFR from baseline (95%CI)				
Day29 (Pre-Dose 2)				
n				
GMT (95%CI)				
Seroconversion % (95%CI)				
GMFR from baseline (95%CI)				
Day36				
n				
GMT (95%CI)				
Seroconversion % (95%CI)				
GMFR from baseline (95%CI)				
Day61				
n				
GMT (95%CI)				
Seroconversion % (95%CI)				
GMFR from baseline (95%CI)				
Day121				
n				
GMT (95%CI)				
Seroconversion % (95%CI)				
GMFR from baseline (95%CI)				
Day394				
n				
GMT (95%CI)				
Seroconversion % (95%CI)				
GMFR from baseline (95%CI)				

Table 8 Summaries of Serum rabies GP IgG RFFIT and ELISA by Study Day and Treatment Group

Treatment Group	**Group A**	**Group B**	**Group C**	**Group D**
Product	Low Dose	Medium Dose	High Dose	Control
Rapid Fluorescent Foci Inhibition Test				
Day 1, n=				
GMT (95% CI)				
% seroprotected (95% CI)				
Day 8, n=				
GMT (95% CI)				
% seroprotected (95% CI)				
% seroconversion (95% CI)				
GMFR (95% CI)				
Day 29, n=				
GMT (95% CI)				
% seroprotected (95% CI)				
% seroconversion (95% CI)				
GMFR (95% CI)				
Day 36, n=				
GMT (95% CI)				
% seroprotected (95% CI)				
% seroconversion (95% CI)				
GMFR (95% CI)				
Day 61, n=				
GMT (95% CI)				
% seroprotected (95% CI)				
% seroconversion (95% CI)				
GMFR (95% CI)				
Day 121, n=				
GMT (95% CI)				
% seroprotected (95% CI)				
% seroconversion (95% CI)				
GMFR (95% CI)				
Day 394, n=				
GMT (95% CI)				
% seroprotected (95% CI)				
% seroconversion (95% CI)				
GMFR (95% CI)				
ELISA				
Day 1, n=				
GMT (95% CI)				
Day 8, n=				
GMT (95% CI)				
% seroconversion (95% CI)				
GMFR (95% CI)				
Day 29, n=				
GMT (95% CI)				
% seroconversion (95% CI)				

GMFR (95% CI)				
Day 36, n=				
GMT (95% CI)				
% seroconversion (95% CI)				
GMFR (95% CI)				
Day 61, n=				
GMT (95% CI)				
% seroconversion (95% CI)				
GMFR (95% CI)				
Day 121, n=				
GMT (95% CI)				
% seroconversion (95% CI)				
GMFR (95% CI)				
Day 394, n=				
GMT (95% CI)				
% seroconversion (95% CI)				
GMFR (95% CI)				

Table 9 Overall Summary of Adverse Events

Subjects with	Group A Number (%)	Group B Number (%)	Group C Number (%)	Group D Number (%)	Overall Number (%)
At least one local solicited adverse event					
At least one systemic solicited adverse event					
At least one unsolicited adverse event					
At least one related unsolicited adverse event					
None (Grade 0)					
Mild (Grade 1)					
Moderate (Grade 2)					
Severe (Grade 3)					
Potentially life-threatening (Grade 4)					
Death (Grade 5)					
At least one severe (Grade 3) unsolicited adverse event					
Related					
Unrelated					
At least one serious adverse event					
At least one adverse event leading to early termination					
At least one medically attended adverse event					
At least one new onset chronic medical condition					
At least one potentially immune mediated medical condition					

Table 10 Number and Percentage of Subjects Experiencing Solicited Events by Symptom and Treatment Group (Safety Population)- IMMEDIATE after the first vaccine dose

Symptom	Group A Number (%)	Group B Number (%)	Group C Number (%)	Group D Number (%)	Overall Number (%)
Any Symptom					
Any Local Symptom					
Warmth					
Tenderness					
Itching					
Pain					
Redness					
Swelling					
Any Systemic Symptom					
Feverishness					
Joint pain					
Body aches/muscular pain					
tiredness					
nausea					
headache					

Table 11 Number and Percentage of Subjects Experiencing Solicited Events by Symptom and Treatment Group (Safety Population)- After the first vaccine dose

Symptom	Group A Number (%)	Group B Number (%)	Group C Number (%)	Group D Number (%)	Overall Number (%)
Any Symptom					
Any Local Symptom					
Warmth					
Tenderness					
Itching					
Pain					
Redness					
Swelling					
Any Systemic Symptom					
Feverishness					
Joint pain					
Body aches/muscular pain					
tiredness					
nausea					
headache					

Table 12 Number and Percentage of Subjects Experiencing Solicited Events by Symptom and Treatment Group (Safety Population)- IMMEDIATE after the second vaccine dose

Symptom	Group A Number (%)	Group B Number (%)	Group C Number (%)	Group D Number (%)	Overall Number (%)
Any Symptom					
Any Local Symptom					
Warmth					
Tenderness					
Itching					
Pain					
Redness					
Swelling					
Any Systemic Symptom					
Feverishness					
Joint pain					
Body aches/muscular pain					
tiredness					
nausea					
headache					

Table 13 Number and Percentage of Subjects Experiencing Solicited Events by Symptom and Treatment Group (Safety Population)- After the second vaccine dose

Symptom	Group A Number (%)	Group B Number (%)	Group C Number (%)	Group D Number (%)	Overall Number (%)
Any Symptom					
Any Local Symptom					
Warmth					
Tenderness					
Itching					
Pain					
Redness					
Swelling					
Any Systemic Symptom					
Feverishness					
Joint pain					
Body aches/muscular pain					
tiredness					
nausea					
headache					

Table 14 Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity and Treatment Group (Safety Population)- IMMEDIATE after the first vaccine dose

Symptom	Severity	Group A Number (%)	Group B Number (%)	Group C Number (%)	Group D Number (%)	Overall Number (%)
Any Symptom	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					
Any Local Symptom	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					
Warmth	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					
Tenderness	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					
Itching	None					
	Mild					
	Moderate					
	Severe					

	Potentially Life Threatening					
Pain	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					
Redness	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					
Swelling	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					
Any Systemic Symptom	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					
Feverishness	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					
Joint pain	None					
	Mild					

	Moderate					
	Severe					
	Potentially Life Threatening					
Body aches/muscular pain	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					
Tiredness	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					
Nausea	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					
Headache	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					

Table 15 Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity and Treatment Group (Safety Population)-After the first vaccine dose

Symptom	Severity	Group A Number (%)	Group B Number (%)	Group C Number (%)	Group D Number (%)	Overall Number (%)
Any Symptom	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					
Any Local Symptom	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					
Warmth	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					
Tenderness	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					
Itching	None					
	Mild					
	Moderate					
	Severe					

	Potentially Life Threatening					
Pain	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					
Redness	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					
Swelling	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					
Any Systemic Symptom	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					
Feverishness	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					
Joint pain	None					
	Mild					

	Moderate					
	Severe					
	Potentially Life Threatening					
Body aches/muscular pain	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					
Tiredness	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					
Nausea	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					
Headache	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					

Table 16 Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity and Treatment Group (Safety Population)–IMMEDIATE after the second vaccine dose

Symptom	Severity	Group A Number (%)	Group B Number (%)	Group C Number (%)	Group D Number (%)	Overall Number (%)
Any Symptom	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					
Any Local Symptom	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					
Warmth	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					
Tenderness	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					
Itching	None					
	Mild					
	Moderate					
	Severe					

	Potentially Life Threatening					
Pain	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					
Redness	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					
Swelling	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					
Any Systemic Symptom	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					
Feverishness	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					
Joint pain	None					

	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					
Body aches/muscular pain	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					
Tiredness	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					
Nausea	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					
Headache	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					

Table 17 Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity and Treatment Group (Safety Population)-After the second vaccine dose

Symptom	Severity	Group A Number (%)	Group B Number (%)	Group C Number (%)	Group D Number (%)	Overall Number (%)
Any Symptom	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					
Any Local Symptom	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					
Warmth	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					
Tenderness	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					
Itching	None					
	Mild					
	Moderate					
	Severe					

	Potentially Life Threatening					
Pain	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					
Redness	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					
Swelling	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					
Any Systemic Symptom	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					
Feverishness	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					
Joint pain	None					
	Mild					

	Moderate					
	Severe					
	Potentially Life Threatening					
Body aches/muscular pain	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					
Tiredness	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					
Nausea	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					
Headache	None					
	Mild					
	Moderate					
	Severe					
	Potentially Life Threatening					

Table 18 Summary of Subjects with Prior or Concurrent Medical Conditions by MedDRA® System Organ Class and Treatment Group

MedDRA® System Organ Class	**MedDRA® Preferred Term**	Group A Number (%)	Group B Number (%)	Group C Number (%)	Group D Number (%)
Any SOC	Any PT				
[SOC1]	Any PT				
	[PT1]				
	[PT2]				
[SOC2]	Any PT				
	[PT1]				
	[PT2]				
Any SOC	Any PT				
[SOC1]	Any PT				
	[PT1]				

Table 19 Summary of Unsolicited Adverse Events and Laboratory Abnormalities by Treatment Group

Treatment Group	**Group A**	**Group B**	**Group C**	**Group D**
Product	Low Dose	Medium Dose	High Dose	Control
Participants reporting unsolicited adverse events from Day 1 through Day 61				
Participants, n=				
Any events, n (%)				
Any Grade ≥2 events, n (%)				
Participants experiencing any Serious Adverse Events through Day 394				
Participants, n=				
Any events, n (%)				
Participants experiencing any Medically Attended Adverse Events through Day 394				
Participants, n=				
Any events, n (%)				
Any Grade ≥2 events, n (%)				
Participants experiencing any New-Onset Chronic Medical Conditions through Day 394				
Participants, n=				
Any events, n(%)				
Participants experiencing any Potential Immune-Mediated Medical Conditions through Day 394				
Participants, n=				
Any events, n(%)				
Participants experiencing new onset sensorineural hearing loss through Day 394				
Participants, n=				
Any events, n(%)				
Participants experiencing clinical laboratory adverse events through Day 61				
Participants, n=				
Any events, n(%)				
Any Grade ≥2 events, n(%)				

Table 20 Number and Percentage of Subjects Experiencing Unsolicited Adverse Events by MedDRA® System Organ Class and Preferred Term, Maximum Severity, Relationship, and Treatment Group–Safety Population

Treatment Group	MedDRA® System Organ Class	MedDRA® Preferred Term	Any Incidence		Severity						Relationship to Treatment			
					Mild		Moderate		Severe		Not Related		Related	
			n	%	n	%	n	%	n	%	n	%	n	%
Group A.(N=X)	Any SOC	Any PT	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	[SOC1]	Any PT												
		[PT1]												
		[PT2]												
	[SOC2]	Any PT												
		[PT1]												
		[PT2]												
Group B:(N=X)	Any SOC	Any PT	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	[SOC1]	Any PT												
		[PT1]												
		[PT2]												
	[SOC2]	Any PT												
		[PT1]												
		[PT2]												
Group C.(N=X)	Any SOC	Any PT	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	[SOC1]	Any PT												
		[PT1]												
		[PT2]												
	[SOC2]	Any PT												
		[PT1]												
		[PT2]												

Group D (N=X)	Any SOC	Any PT	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	[SOC1]	Any PT												
		[PT1]												
		[PT2]												
	[SOC2]	Any PT												
		[PT1]												
		[PT2]												

Table 21 Number and Percentage of Subjects Experiencing Non-Serious Related Unsolicited Adverse Events by MedDRA® System Organ Class and Preferred Term, Maximum Severity, and Treatment Group

Treatment Group	MedDRA® System Organ Class	MedDRA® Preferred Term	Any Incidence		Severity					
					Mild		Moderate		Severe	
			n	%	n	%	n	%	n	%
Group A:(N=X)	Any SOC	Any PT	x	xx	x	xx	x	xx	x	xx
	[SOC1]	Any PT	x	xx	x	xx	x	xx	x	xx
		[PT1]								
		[PT2]								
	[SOC2]	Any PT								
		[PT1]								
		[PT2]								
Group B:(N=X)	Any SOC	Any PT	x	xx	x	xx	x	xx	x	xx
	[SOC1]	Any PT	x	xx	x	xx	x	xx	x	xx
		[PT1]								
		[PT2]								
	[SOC2]	Any PT								
		[PT1]								
		[PT2]								
Group C:(N=X)	Any SOC	Any PT	x	xx	x	xx	x	xx	x	xx
	[SOC1]	Any PT	x	xx	x	xx	x	xx	x	xx
		[PT1]								
		[PT2]								
	[SOC2]	Any PT								

		[PT1]								
		[PT2]								
Group D:(N=X)	Any SOC	Any PT	x	xx	x	xx	x	xx	x	xx
	[SOC1]	Any PT	x	xx	x	xx	x	xx	x	xx
		[PT1]								
		[PT2]								
	[SOC2]	Any PT								
		[PT1]								
		[PT2]								

Listing 1 Listing of Subjects Receiving Investigational Product

Subject ID	Randomized Treatment Group	Product Received Study Dose 1	Product Received Study Dose 2

Listing 2 Early Terminations or Discontinued Subjects

Subject ID	Treatment Group	Category	Reason for Early Termination or Treatment Discontinuation	Study Day

Listing 3 Subject-Specific Protocol Deviations

Subject ID	Treatment Group	Deviation Number	Deviation	Deviation Category	Study Day	Reason for Deviation	Deviation Resulted in AE?	Deviation Resulted in Subject Termination?	Deviation Affected Product Stability?	Deviation Resolution	Comments

Listing 4 Non-Subject-Specific Protocol Deviations

Site	Deviation	Start Date	End Date	Reason for Deviation	Deviation Resulted in Subject Termination	Deviation Affected Product Stability?	Deviation Category	Deviation Resolution	Comments

Listing 5 Subjects Excluded from Analysis Populations

Treatment Group	Subject ID	Analyses in which Subject is Included	Analyses from which Subject is Excluded	Results Available?	Reason Subject Excluded

Note: "Yes" in the "Results available" column indicates that available data were removed from the analysis. "No" indicates that no data were available for inclusion in the analysis.

Listing 6 Demographics Data

Subject ID	Treatment Group	Sex	Age at Enrollment (years)	Ethnicity	Race	BMI

Listing 7 Pre-Existing and Concurrent Medical Conditions

Subject ID	Treatment Group	MH Number	Medical History Term	Condition Start Day	Condition End Day	MedDRA® System Organ Class	MedDRA® Preferred Term

Listing 8 Individual Immunogenicity Response Data

Subject ID	Treatment Group	Planned Time Point	Actual Study Day	Assay	Titer

Listing 9 Solicited Events– Local Symptoms

Subject ID	Treatment Group	Dose Number	Post Dose Day	Symptom	Severity

Listing 10 Solicited Events–Systemic Symptoms

Subject ID	Treatment Group	Dose Number	Post Dose Day	Assessment	Symptom	Severity

Listing 11 Unsolicited Adverse Events

Adverse Event	Associated w/ Dose #	# of Days Post Associated Dose (Duration)	Severity	SAE Y/N	MAAE Y/N	PIMMC Y/N	NOCMC Y/N	AESI Y/N	Relationship to Study Treatment	If Not Related, Alternative Etiology	Action Taken With Study Treatment	Subject Discontinued Due to AE	Outcome	MedDRA® System Organ Class	MedDRA® Preferred Term
Subject ID:, Treatment Group:, AE Number															

Listing 12 Narratives of Deaths, Other Serious and Significant Adverse Events

Listing 13 Clinical Laboratory Adverse Events

Number	Subject ID	Cohort	Visit No.	No. days post-vaccination	Clinical Safety Laboratory Test	Value	Severity	Related/Not Related
1								

Listing 144 Concomitant Medications

Subject ID	Treatment Group	CM Number	Medication	Medication Start Day	Medication End Day	Indication	Taken for an AE? (AE Number)	Taken for a condition on Medical History? (MH Number)

Listing 15Pregnancy Reports– Maternal Information

Subject ID	Treatment Group	Pregnancy Number	Study Day Corresponding to Estimated Date of Conception	Source of Maternal Information	Pregnancy Status	Mother's Pre-Pregnancy BMI	Mother's Weight Gain During Pregnancy	Tobacco, Alcohol, or Drug Use During Pregnancy?	Medications During Pregnancy?	Maternal Complications During Pregnancy?	Maternal Complications During Labor, Delivery, or Post-Partum?

Listing 16 Pregnancy Reports– Gravida and Para

			Live Births												
Subject ID	Pregnancy Number	Gravida	Extremely PB	Very Early PB	Early PB	Late PB	Early TB	Full TB	Late TB	Post TB	Still Births	Spontaneous Abortion/ Miscarriage	Elective Abortions	Therapeutic Abortions	Major Congenital Anomaly with Previous Pregnancy?

Listing 17 Pregnancy Reports– Live Birth Outcomes

Subject ID	Pregnancy Number	Fetus Number	Pregnancy Outcome (for this Fetus)	Fetal Distress During Labor and Delivery?	Delivery Method	Gestational Age at Live Birth	Size for Gestational Age	Apgar Score, 1 minute	Apgar Score, 5 minutes	Cord pH	Congenital Anomalies?	Illnesses/ Hospitalizations within 1 Month of Birth?

Listing 188 Pregnancy Reports– Still Birth Outcome

Subject ID	Date of Initial Report	Fetus Number	Pregnancy Outcome (for this Fetus)	Fetal Distress During Labor and Delivery?	Delivery Method	Gestational Age at Still Birth	Size for Gestational Age	Cord pH	Congenital Anomalies?	Autopsy Performed?	If Autopsy, Etiology for Still Birth Identified?

Listing 19 Pregnancy Reports– Spontaneous, Elective, or Therapeutic Abortion Outcomes

Subject ID	Date of Initial Report	Fetus Number	Pregnancy Outcome (for this Fetus)	Gestational Age at Termination	Abnormality in Product of Conception?	Reason for Therapeutic Abortion