A Phase 1, Randomized Trial to Assess the Safety, Reactogenicity, and Immunogenicity of a Combination HTNV and PUUV DNA Vaccine Candidate Administered by Electroporation

Statistical Analysis Plan

Version 4.0

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LIST OF ABBREVIATIONS

AE	Adverse Effect
CI	Confidence Interval
CSR	Clinical Study Report
DMID	Division of Microbiology and Infectious Diseases, NIH
DNA	Deoxyribonucleic Acid
eCRF	Electronic Case Report Form
EP	Electroporation
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMT	Geometric Mean Titer
HIV	Human Immunodeficiency Virus
HTNV	Hantaan Virus
ICH	International Conference on Harmonisation
ID	Intradermal (ly)
IM	Intramuscular (ly)
IRB	Institutional Review Board
ISM	Independent Safety Monitor
MedDRA	Medical Dictionary for Regulatory Activities
N	Sample Size
ORP	Office for Research Protections
ORA	Office of Regulated Activities
PI	Principal Investigator
PSSB	Product Safety Surveillance Branch
PsV	Pseudovirions
PsVNA	Pseudovirion Neutralization Assay
PUUV	Puumala Virus

PVG	Pharmacovigilance
RA	Regulatory Affairs
RM	Research Monitor
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SRC	Safety Review Committee
TDS-EP	TriGrid Delivery System for Epidermal Delivery
TDS-ID	TriGrid Delivery System for Intradermal Delivery
TDS-IM	TriGrid Delivery System for Intramuscular Delivery
UMB	University of Maryland Baltimore
USAMRIID	US Army Medical Research Institute of Infectious Diseases
USAMRMC	US Army Medical Research and Materiel Command
USAMMDA	US Army Medical Materiel Development Activity
WRAIR	Walter Reed Army Institute of Research

1. PREFACE

The Statistical Analysis Plan (SAP) for "A Phase 1, Randomized Trial to Assess the Safety, Reactogenicity, and Immunogenicity of a Combination HTNV and PUUV DNA Vaccine Candidate Administered by Electroporation" describes and elaborates on the statistical outline provided in the study protocol. Text in the SAP makes reference to the Protocol, and hence, is recommended that the two are read in companion. This SAP overviews the purpose for and nature of the trial methodology. Additionally, tables, figures, and lists that will appear in the final report are previewed.

The SAP is written in the format outlined by the FDA and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines, particularly Topics E3, E8, and E9. Furthermore, all work planned and reported for this SAP will follow statistical practice guidelines published by the American Statistical Association and the Royal Statistics Society.

The SAP is organized as follows: Sections 3-5 will review the study design, Sections 6-7 will cover general statistical considerations and subject disposition, Sections 8-9 will discuss in detail the statistical analysis methods, and Section 10-11 will cover reporting conventions and technical details. The Appendices are comprised of Appendix I: Tables; Appendix II: Figures; and Appendix III: Listings. Deviations from this SAP will be discussed and justified in the final CSR.

2. INTRODUCTION

2.1. Purpose of the Analyses

This open-label study aims to evaluate the safety, reactogenicity, and immunogenicity of the hantaan virus (HTNV), puumala virus (PUUV), and combination HTNV/PUUV DNA vaccine candidates delivered to healthy adults either intramuscularly (IM) or intradermally (ID) by electroporation (EP).

While this plan as written constitutes the analysis and methodological intentions at the time of its writing, the study team reserves the right to make any proper adjustments after a blind review of the data.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Primary Objective

- To evaluate the safety and reactogenicity of the hantaan virus (HTNV), puumala virus (PUUV), and combination HTNV/PUUV DNA vaccine candidates delivered to healthy adults either intramuscularly (IM) or intradermally (ID) by electroporation (EP).

3.2. Secondary Objectives

- To obtain a preliminary assessment of the immunogenicity of the combination HTNV/PUUV DNA vaccine candidate relative to the monovalent formulations.
- To identify the HTNV and/or PUUV DNA vaccine combination and route of administration that elicits the most immunogenic response as determined by seroconversion and seropositivity rates, and geometric mean titers (GMT) as measured by PsVNA50.

3.3. Primary Endpoints

The primary endpoints align with the safety objective. The nature, frequency, and severity of adverse events (AEs) and/or serious adverse events (SAEs) associated with TDS-EP-based administration of HTNV and PUUV DNA vaccines.

- The occurrence of solicited local and systemic AEs occurring from the time of each injection through 14 days following the procedure (memory aid to assist with the first 14 days)
- The occurrence of vaccine-related unsolicited AEs from the time of the first injection through 28 days following each injection
- The occurrence of SAEs from the time of the first injection through the final study visit for each subject (approximately 6 months post-last vaccination)
- The occurrence of clinical safety laboratory AEs through 14 days following each study vaccination.

3.4. Secondary Endpoints

The secondary endpoints align with the immunogenicity objectives.

Secondary endpoints, correlating to the secondary objectives of the study will be to determine the proportion of seropositive subjects (PsVNA50 ≥ 1:20) and the final overall rate of seroconversion over all scheduled time points to study completion for each study group. GMT will be calculated using PsVNA50.

- Determination of the proportion of seropositive subjects (defined as PsVNA50 ≥ 1:20) at each scheduled time point (eg, Days 0, 28, 56, 84, 140, and 220)
- Determination of the final overall rate of seroconversion over all scheduled time points to study completion for each study group. Seroconversion is defined as a post-vaccination HTNV- or PUUV-specific titer of ≥ 1:40, or a minimum four-fold rise compared to baseline titer, and all study volunteers will begin the study with a baseline titer < 20 (ie, seronegative).
- Determination of GMT of the PsVNA50 for HTNV- and PUUV-specific neutralizing antibodies at each scheduled time point for each study group and over all time points for each study group.

Exploratory endpoints:

Exploratory endpoints, evaluated as part of the immunogenicity objectives, including calculation of PsVNA80 titers for HTNV and PUUV may be calculated from the collected data for informational purposes, and neutralization assays using other hantavirus PsV (eg, Seoul virus, Dobrava virus) may also be performed to evaluate levels of cross-neutralizing antibodies.

- Determination of GMT of neutralizing of the PsVNA80 for HTNV- and PUUV-specific neutralizing antibodies at each scheduled time point for which blood samples are taken for each study group and over all time points for each study group
- Determination of GMT of neutralizing of the PsVNA50 and 80 for Seoul- and Dobrava-specific neutralizing antibodies at each scheduled time point for which blood samples are taken for each study group and over all time points for each study group

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

The study design, including doses and schedule, is based on the experience of a team of investigators to include personnel at USAMMDA (now ORA), USAMRIID, Ichor, and WRAIR, who have performed clinical trials with similar DNA vaccine constructs using Ichor's TDS-IM EP device for DNA vaccinations. These TDS-IM and TDS-ID EP devices have been tested in humans previously in a recent clinical trial to evaluate the safety and immunogenicity of a DNA vaccine for Venezuelan encephalitis virus. These same HTNV and PUUV DNA vaccine products have also been tested in humans previously, albeit only using the TDS-IM EP device, and at lower dose levels than proposed in this study. Previous studies examined these vaccines in Phase 1 and 2 clinical trials at up to 2-mg dose levels per IM EP administration, whereas this study is testing up to 6 mg of DNA per administration using the 2 devices. The GLP repeat-dose rabbit toxicology and immunogenicity study performed in support of this study administered these same HTNV and PUUV DNA vaccines at up to 6 mg doses using the 2 devices and at an increased dosing frequency compared to this proposed Phase 1 clinical trial design. The rabbit toxicology study did not reveal safety concerns for the use of this higher dose level and with these 2 devices.

This study will be a single-center, randomized, study of the HTNV, PUUV, and combined HTNV/PUUV DNA vaccines delivered IM and ID by EP.

Pending sentinel group outcomes (elaboration in Section 4.2.1), the study will enroll up to 6 randomized groups of up to 12 subjects each for a total of up to 72 subjects (12 enrolled in effort to ensure at least 10 will complete per group). The HTNV and PUUV DNA vaccines will be administered to subjects as follows:

Group 1: 0.6 mg HTNV by ID EP

Group 2: 3.0 mg HTNV by IM EP

Group 3: 0.6 mg PUUV by ID EP

Group 4: 3.0 mg PUUV by IM EP

Group 5: 1.2 mg HTNV/PUUV by ID EP

Group 6: 6.0 mg HTNV/PUUV by IM EP

Every subject will receive 1 injection on Days 0, 28, and 56 for a total of 3 injections, and subjects will be followed up to 6-months after the final vaccination (to Day 220). Four of the six study groups include sentinel subjects because the dose of investigational product (IP) has not been evaluated in human subjects, and we would like to evaluate the safety of the IP dose before the remainder of the subjects from the respective group are dosed. Sentinel subjects will not be used for Groups 1 and 3 because the IP dose is lower than the 2.0 mg/mL dose that was previously evaluated in human subjects.

Dosing for sentinels and main study subjects will progress as follows:

For Groups 2 and 4, the first dose will be given to four sentinel subjects (n = 2 per group, total of 4 subjects) on the same day, and those four subjects will be followed for 48 hours as per the Sentinel Group Halting Rules. The SRC will meet and evaluate the safety data collected in the 48-hour period post-vaccination for sentinels in Groups 2 and 4. If the SRC finds that a halting rule(s) has been met, the PI will notify ORA PSSB within 24 hours. A Safety Monitoring Committee (SMC) meeting will be held to review clinical and laboratory safety and reactogenicity data. In the presence of a safety signal, no additional volunteers will be enrolled to Groups 2 and 4, and 24 volunteers will be enrolled and equally randomized to Groups 1 and 3 (n=12 per group). In the absence of a safety signal, enrollment and randomization of additional volunteers in Groups 2 and 4 (n=10 per group, total of 20) for the first dose (Day 0) will commence. Subjects in Groups 2 and 4 will be evaluated for 48-hours post-vaccination for any halting criteria on the Day 2 clinic visit.

After the first dose for all subjects in Groups 2 and 4 has been successfully completed and none of the halting criteria are met, then the first dose will be given to four sentinel subjects in Groups 5 and 6 (n=2 per group, total of 4 subjects) on the same day, and those four subjects will be followed for 48 hours as per the Sentinel Group Halting Rules. The SRC will meet and evaluate the safety data collected in the 48-hour period post-vaccination for sentinels in Groups 5 and 6. If the SRC finds that the halting rules have been met, the PI will notify ORA PSSB within 24 hours. A SMC meeting will be held to conduct a review of clinical and laboratory safety and reactogenicity data. In the presence of a safety signal, no additional volunteers will be enrolled to Groups 5 and 6, and 24 volunteers will be enrolled and equally randomized to Groups 1 and 3 (n=12 per group). In the absence of a safety signal, enrollment, randomization and vaccination (Day 0) of additional volunteers in Groups 5 and 6 (n=10 per group) plus Groups 1 and 3 (n=12 per group) will commence. Subjects in Groups 5 and 6 and 1 and 3 will be evaluated for the 48-hours post-vaccination for any halting criteria on the Day 2 clinic visit.

At this time, all groups will have received the first dose and the trial will advance through the prescribed visits and additional vaccinations. Subjects are expected to complete a total of 12 visits (not including screening). Overall study duration is expected to be approximately 11 months.

4.1.1. Study Halting Criteria

Further enrollment and study vaccinations will be halted for SMC review/recommendation if any of the following are reported:

- Any subject experiences a study product-related SAE from the time of the study product administration through the subject's last study visit.
- Any subject experiences laryngospasm, bronchospasm, or anaphylaxis within 1 day after administration of study product that is considered related to study product.
- Two or more subjects experience generalized urticaria (defined as occurring at more than 2 body parts) within 3 days after administration of study product that is considered related to study product.

This trial will also be halted for SMC review/recommendation if, within 7 days after administration of any study vaccination, any of the following occurs:

- Two or more subjects experience a Grade 3 unexpected AE in the same MedDRA system organ class (captured by preferred term) after administration of study product that is considered related to study product and not resolved or improved to lower grade within 2 days.
- Two or more subjects experience the same Grade 3 solicited local adverse event that is considered related to study product and not resolved or improved to lower grade within 2 days.
- Two or more subjects experience the same Grade 3 solicited systemic adverse event that is considered related to study product and not resolved or improved to lower grade within 2 days.
- Two or more subjects experience the same Grade 3 laboratory adverse event that is considered related to study product.

Grading scales for solicited local (application site) and systemic (subjective and quantitative) AEs are included in Protocol Section 11.5 and Appendix C.

Grading scales for clinical safety laboratory adverse events are included in Protocol Section 11.5 and Appendix C.

4.1.2. Sentinel Group Safety Criteria

The following halting rules will be applied in the 48 hours following sentinel group vaccination (n = 2 subjects per cohort) for review by the SRC and if any are met, the PI will notify ORA PSSB within 24 hours and further vaccinations will be halted pending SMC review:

- Any SAE regardless of the relationship to the vaccine (with the exception of death or hospitalization that was the result of trauma or accident)
- Type 1 hypersensitivity reaction (anaphylaxis or generalized urticarial)
- Any Grade 3 systemic adverse event (solicited and unsolicited)
- Any Grade 3 local adverse event (solicited and unsolicited) that has not reduced to a Grade 1 or 2 at 48 hours post vaccination*

*Injection site pain (if resolved 48 hours post vaccination), the size (measured in mm) of erythema, and the occurrence of induration/swelling will not be used as halting criteria.

4.2. Measures Taken to Minimize/Avoid Bias

4.2.1. Randomization

Randomization will take up to four stages, depending on which of four scenarios is determined by sentinel group analysis. Groups 2 and 4 and also 5 and 6 have sentinels as part of the study design because these groups are highest doses offered. Groups 1 and 3 do not have sentinel subjects. If any sentinel testing halts Groups 2, 4, 5 or 6, then Groups 1 and 3 can proceed. It is the study team's preference to test Groups 1 and 3 at the end, assuming Scenario 4 is feasible, so the workflow has been described to enroll as many participants as possible from Groups 5, 6, 1 and 3 at the same time.

Stage 1: Four sentinel subjects are randomly assigned to either Group 2 or 4 with a 1:1 allocation ratio to form the first two sentinel groups (i.e., 2 sentinel subjects per group).

Trial Enrollment Scenario 1 (N=28):

If sentinel halting criteria are met after Stage 1, no additional participants will be assigned to Groups 2 or 4, and no participants will be assigned to Groups 5 or 6. An additional set of 24 participants will be equally randomized into Groups 1 or 3 using a permuted block randomization with a block size of 6. Hence a total of 28 participants (12 in Group 1, 2 in Group 2, 12 in Group 3, and 2 in Group 4) will be enrolled in the trial in this scenario.

Stage 2: If no halting criteria are met for Groups 2 and 4 with n=2 sentinels per group, then additional 20 subjects will be enrolled and randomized into Groups 2 and 4 (n=10 more participants per group, for a total of n=12 per group). At this time there will be 24 participants randomized into Groups 2 and 4.

Trial Enrollment Scenario 2 (N=48):

If study halting criteria are met after Stage 2, no participants will be assigned to Groups 5 or 6. An additional set of 24 participants will be equally randomized into Groups 1 or 3 using a permuted block randomization with a block size of 6. Hence a total of 48 participants (12 in Group 1, 12 in Group 2, 12 in Group 3, and 12 in Group 4) will be enrolled in this scenario.

Stage 3: If no halting criteria are met by the completion of Stages 1 and 2, four sentinel subjects will be randomly assigned to either Group 5 or 6 with a 1:1 allocation ratio to form two additional sentinel groups (i.e., 2 sentinel subjects per group).

Trial Enrollment Scenario 3 (N=52):

If halting criteria are met after Stage 3, an additional set of 24 participants will be enrolled and equally randomized into Groups 1 or 3 using a permuted block randomization with a block size of 6. Hence a total of 52 participants (12 in Group 1, 12 in Group 2, 12 in Group 3, 12 in Group 4, 2 in Group 5, and 2 in Group 6) will be enrolled in the trial in this scenario.

Stage 4: If no halting criteria are met for Groups 5 and 6 with n=2 sentinels per group, then additional 20 subjects will be enrolled and randomized into Groups 5 and 6 (n=10 more participants per group, for a total of n=12 per group), and an additional set of 24 participants will be enrolled and equally randomized into Groups 1 and 3 at the same time. This is the ideal scenario for workflow and efficiency at CVD.

Trial Enrollment Scenario 4 (N=72):

If halting criteria are not met after Stage 3, an additional set of 40 participants will be equally randomized into Groups 1,3,5 and 6 using a permuted block randomization with a block size of 8 and an additional of 4 participants will be randomized into Group 1 or 3 to achieve a total of 12 participants per group. Hence a total of 72 participants (6 groups, 12 per group) will be enrolled in the trial in this scenario.

A single document delineating the randomized assignment of subjects to vaccine groups for various scenarios described above will be pre-generated by the study statistician and maintained in a secure location as part of the regulatory file. During the study, investigators, research coordinators, University of Maryland's IDS, representatives of the sponsor and applicable regulatory authorities will have access to this list if required by their duties.

4.2.2. Blinding

Clinical staff and subjects are not blinded during the trial. Samples sent to the immunogenicity lab at USAMRIID will not be identified as to subject ID or Group ID, therefore those samples, data collection and lab analysis at the site will be collected under blinded conditions to avoid introducing bias in the immunogenicity data.

4.3. Study Sample

The study sample will consist of up to 72 healthy male and nonpregnant, nonlactating female subjects, ages 18 to 49 years (inclusive), who are HTNV and PUUV naïve (i.e., up to 12 subjects per group). The intended study sample for the study is 60 participants (i.e., 10 subjects per group). Due to attrition concerns, an additional 2 participants will be enrolled to each group to bring the total study sample to 72. Please refer to Section 5 for details on the relationship between the sample size and expected power of analyses.

4.4. Eligibility Screening

Each eligible subject must meet all inclusion and no exclusion criteria. Subjects who have signed the informed consent form and completed the assessment of understanding will provide a medical history and undergo a physical examination and routine laboratory screening tests. The PI or designee will make the final decision of the eligibility. Only eligible subjects will be given the investigational product.

4.5. Subject Inclusion Criteria

Subjects must meet all of the following criteria to be included in the study:

- Healthy adult male or nonpregnant, nonlactating female, ages 18-49 (inclusive) at time of screening.
- Have demonstrated adequate comprehension of the protocol by achieving a score of at least 80% correct on a short multiple-choice quiz. Individuals who fail to achieve a passing score on the initial quiz will be given the opportunity to retest after a review of protocol information. Individuals who fail the quiz for the second time will not be enrolled.

- Have provided written informed consent before screening.
- Free of clinically significant health problems, in the opinion of study investigators, as determined by pertinent medical history and clinical examination before entry into the study.
- Available and able to participate for all study visits and procedures.
- Sexually active men* and women of childbearing potential** must agree to use an effective method of contraception from 30 days prior to the first study vaccination until 6 months after the last study vaccination.
  - *A sexually active man is defined as one whose partner is a woman of childbearing potential (see definition below) and has not had a vasectomy performed > 1 year prior to screening. They must agree not to father a child until 6 months after the last vaccination. These subjects must agree to use a barrier method of birth control (eg, either condom with spermicidal foam/gel/film/cream or partner usage of occlusive cap [diaphragm or cervical/vault caps] with spermicidal foam/gel/film/cream/suppository).
  - **Women of childbearing potential are defined as those who have not been sterilized via tubal ligation, bilateral oophorectomy, bilateral salpingectomy, hysterectomy, or successful Essure® placement (permanent, non-surgical, non-hormonal sterilization) with history of documented radiological confirmation test at least 90 days after the procedure (or with use of another birth control method if history of confirmation test not confirmed), still menstruating or < 1 year of the last menses if menopausal. For this study, an effective contraceptive method is defined as one that results in a failure rate of less than 1% per year when it is used consistently and correctly (see the Manual of Procedures [MOP] for a list of acceptable methods).
- Female subjects agree to not donate eggs (ova, oocytes), and male subjects agree to not donate sperm from the start of screening until at least 6 months after the last vaccination.
- Female subjects of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test within 24 hours prior to each study vaccination.
- Negative hantavirus PsVNA test result at screening.

4.6. Subject Exclusion Criteria

Subjects meeting any of the following criteria will be excluded from the study:

- History of prior infection with any hantavirus virus or prior participation in an HTNV, PUUV, or Andes virus vaccine trial.
- Has plans to travel to an area with endemic Hantaan, Puumala, Seoul, and Dobrava virus transmission during the study.

  - NOTE: Refer to the MOP for information on areas with endemic Hantaan, Puumala, Seoul, and Dobrava virus transmission.

- History of severe local or systemic reactions to any vaccine or vaccine product* or a history of severe allergic reactions.
  - *This includes a known allergy to an aminoglycoside (eg, gentamicin, tobramycin, neomycin, and streptomycin).
- Is currently participating or plans to participate in another clinical study involving any investigational product (including vaccines) or involves blood drawing, and/or an invasive procedure.*
  - *An invasive procedure includes endoscopy, bronchoscopy, or procedure requiring administration of IV contrast or removal of tissue.
- Receipt or planned receipt of any live vaccination, experimental or otherwise, within the period 30 days prior to or after each vaccination and receipt of an inactivated vaccination, experimental or otherwise, within the period of 14 days prior to or after each vaccination.
- Individuals, who based on clinical assessment by the investigator, have insufficient muscle mass to accommodate the 1 inch/25 mm penetration depth or have a skinfold thickness at eligible injection sites (deltoid region) that exceeds 40 mm.
- Individuals, in whom the ability to observe possible local reactions at the eligible injection sites (deltoid region) is, in the opinion of the investigator, unacceptably obscured due to a physical condition or permanent body art. Presence of any surgical or traumatic metal implants at the site of administration (medial deltoid muscles or overlying skin).Screening laboratory results that are outside of the normal range (exceptions listed below) within 56 days prior to enrollment.
- Hemoglobin > 11.0 g/dL for women; > 12.9 g/dL for men
- CBC (WBC and platelet) with differential either within institutional normal range or Grade 1 deviation from normal and deemed clinically insignificant
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 1.25x upper limit of normal (ULN)
- Serum creatinine ≤ ULN
- Subjects with autoimmune disorders or chronic inflammatory disorders with a potential autoimmune correlation.
- Receipt of immunoglobulins and/or any blood products within the 120 days preceding screening or planned administration during the study period.
- Donation of blood to a blood bank within 56 days prior to screening and at any time during the study period.
- Subject seropositive for hepatitis B surface antigen (HBsAg) or hepatitis C antibodies (anti-HCV).

- Any confirmed or suspected immunosuppressive or immunodeficient condition, including HIV infection or use of anticancer chemotherapy or radiation therapy (cytotoxic) in the 3 years prior to screening.
- Administration of chronic (defined as more than 14 days) immunosuppressants or other immune-modifying drugs within 6 months of screening. For corticosteroids, this will mean prednisone, or equivalent, greater than or equal to 5 mg/day. Intranasal, inhaled (< 800 beclomethasone mcg/day), and topical steroids are allowed.
- Has current or past diagnosis of schizophrenia, bipolar disease, or other psychiatric diagnosis that may interfere with subject compliance or safety evaluations.
- Has been hospitalized for psychiatric illness, history of suicide attempt, or confinement for danger to self or others within 10 years prior to screening.
- Any chronic or active neurologic disorder, including Guillain-Barré syndrome, seizures and epilepsy, excluding a single febrile seizure as a child.
- Syncopal episode within 12 months of screening.
- Suspected or known current alcohol and/or illicit drug abuse within the past 5 years based on self-reporting and physical exam.
- Any medical, psychiatric, social condition, occupational reason, or other responsibility that, in the judgment of the investigator, is a contraindication to protocol participation or impairs a subject's ability to give informed consent or to comply with the protocol schedule.
- Pregnant or lactating female, or subject plans to father a child or become pregnant during the study period.
- Current employee or staff paid entirely or partially by the contract for this trial, or staff who are supervised by the PI or subinvestigators.
- Subjects with implanted electronic devices stimulation device, such as cardiac demand pacemakers, automatic implantable cardiac defibrillator, nerve stimulators, or deep brain stimulators.
- Bleeding diathesis or condition associated with prolonged bleeding time, as determined through measurement of PT/PTT (prothrombin time/partial thromboplastin times) during screening labs, that would contraindicate ID or an IM injection.
- History of cardiac arrhythmia or palpitations or abnormal arrhythmia noted on ECG performed at screening (eg, supraventricular tachycardia, atrial fibrillation, frequent ectopy) prior to study entry. Measurement of sinus bradycardia [ie, < 50 beats per minute on exam]) at screening.
- History of diabetes type 1 or 2.

Note: Table 1.1 presents ineligibility summary of screen failures.

4.6.1. Temporary Exclusion Criteria

The following criteria will result in a delay for vaccination of subjects:

- A febrile illness (oral temperature of > 38.0°C) within 48 hours before vaccination or other evolving acute illness.
- Use of antibiotics for an acute illness within 24 hours before the vaccination or any antiviral within 72 hours of study vaccination.
- Use of allergy treatment with antigen injections within 30 days prior to initial study vaccine administration.

4.7. Withdrawal

Termination of dosing is defined as someone who elects to no longer receive doses but is willing to remain on the study for continued observations, immunogenicity assessment and monitoring of safety parameters. Withdrawal from study is defined as not participating this the study any longer, and not continuing to be observed by the study physician. Each subject may withdraw consent for continued dosing or from the study entirely at any time without penalty. Counseling about the subject's health will be provided if he/she decides to discontinue participation in the study. Medical advice regarding what is in the best interest of the subject will be provided.

The PI may discontinue the subject's receipt of investigational product without the subject's consent if any of these criteria is met:

- The discovery or development of any health condition within a subject that would make his or her continued participation in the protocol dangerous to him- or herself.
- The failure of the subject to comply with the requirements of the protocol.
- The scientific integrity of the study may be compromised by further participation.
- Any significant finding that in the opinion of the investigator would increase the risk of the subject having an adverse outcome from further participation in the study.

For example:

- Pregnancy
- Receipt of disallowed licensed vaccine, experimental product or medication
- New onset of illness or condition that meets the Exclusion Criteria
- Medical condition or medication change for which continued participation, in the opinion of the site principal investigator or appropriate sub-investigator, would pose a risk to the subject or would likely confound interpretation of the results.
- Presence of signs or symptoms that could confound or confuse assessment of study vaccine reactogenicity.
- Grade 3 solicited or unsolicited adverse event that is ongoing, whether or not it is improved or resolving. An unresolved or continuing Grade 1 or Grade 2 adverse event is permissible following the documented determination by the site principal

investigator or appropriate sub-investigator, that it would not render study vaccination unsafe or interfere with the evaluation of adverse events or immunologic response.

- Grade 3 solicited or unsolicited adverse event that occurs without alternative etiology in the 7 days following study vaccination.
- Any laryngospasm, bronchospasm, or anaphylaxis within 1 day after administration of study product that is considered related to study product.
- Any generalized urticaria within 3 days after administration of study product that is considered related to study product.
- Serious adverse event related to the study vaccination.
- As deemed necessary by the site principal investigator or appropriate sub-investigator for noncompliance or other reasons.
- Subject refusal of further study vaccination.
- Termination of this trial.
- New information becomes available that makes further administration of the study vaccine unsafe.

All data collected up to the time of withdrawal, including any final evaluation and lab results that may be pending at the time of withdrawal, will be included in the final analysis. All major comparisons between randomized groups will be according to "intent-to-treat" (ITT) principle, that is, participants will be analyzed (and outcomes attributed) according to randomized strategy, regardless of subsequent treatment.

4.8. Route of Administration, Dosage Regimen, Treatment Period, and Justification

Subjects will receive HTNV DNA vaccine, pWRG/HTN-M(co), and PUUV DNA vaccine, pWRG/PUU-M(s2), administered separately and as a mixture using the TDS-IM and TDS-ID devices developed by Ichor Medical Systems, Inc. Subjects will be randomized (See Section 4.2.1) and will receive 1 dose on each of Days 0, 28, and 56 for a total of 3 doses. The vaccine mixing process will be outlined in a supplementary document.

The rationale for dosages and plan of administration is based on prior work by the delivery device manufacturer and prior experience from a previous HTNV DNA and PUUV DNA vaccine study in which candidate vaccines were shown to elicit antibodies in humans when administered by IM EP.

4.9. Investigational Product

The investigational products that will be administered using the TDS-IM or TDS-ID EP device are the HTNV, PUUV, and HTNV/PUUV DNA vaccines given as a single injection. These investigational products were manufactured by Ajinomoto Althea, Inc., San Diego, California. See the study protocol for further information about the investigational products.

5. SAMPLE SIZE CONSIDERATIONS

Because this is a pilot study, all analyses are exploratory. The group sample sizes of up to 12 subjects thus were chosen without the intention that group differences will be detected with a sufficient power.

6. GENERAL STATISTICAL CONSIDERATIONS

6.1. General Principles

The following descriptive statistics will be reported for all continuous variables: sample size (N), mean, median, standard deviation, first quartile, third quartile, maximum, and minimum. For categorical variables, sample size (N), frequency, and percentage will be reported. In addition, data will be reported overall and by treatment group.

6.2. Timing of Analyses

The final analysis will be performed after database lock.

6.3. Analysis Populations

All subjects excluded from the study analysis will be presented in Table 1.2 and Listing 1.1 in Appendix III.

6.3.1. Safety Population

Subjects who receive at least one immunization will comprise the Safety Population, regardless of subsequent withdrawal from study. If the subject permits, she or he will be followed through resolution of any ongoing adverse events. Women who become pregnant during the duration of the study will be encouraged to seek obstetric care and will be asked to provide follow-up information at the conclusion of the pregnancy. These pregnant subjects will be followed for safety and will not receive any additional immunizations. They will be followed for the duration of their pregnancy, and any evidence of fetal harm will be reported promptly to the UMB IRB and sponsor within 24 hours of study team knowledge.

6.3.2. Immunogenicity Population

Subjects who receive at least one immunization and for whom serological data are available will comprise the Immunogenicity Population. If a subject withdraws from the study, all data collected up to the time of withdrawal, including any final evaluation and lab results that may be pending at the time of withdrawal, will be reported. Likewise, any specimens collected up to the time of withdrawal, including any samples collected for storage and use in future research, will be kept and utilized as outlined in the protocol and consent form. A subject may, however, choose to revoke consent for the use of her or his samples, whereby any unused samples will be destroyed.

6.4. Missing Data

No imputations for missing data are planned. For analyses that require study completion, such as the final overall rate of seroconversion for all subjects, subjects who withdrew before the study completion will be excluded.

6.5. Interim Analyses and Data Monitoring

Groups 2, 4, 5, and 6 will each have 2 sentinel subjects who will receive the first vaccination followed by a 48-hour observation period. The sentinel subjects for Groups 2 and 4 will be evaluated prior to continuing with dosing of the rest of Groups 2 and 4, followed by the sentinel subjects for Groups 5 and 6. In the absence of pre-defined criteria and after SRC and/or SMC meetings, the remainder of the cohorts can proceed to vaccination (see Section 4.2.1).

*Note: Sentinel subjects will not be included for Groups 1 and 3 because the dose is lower than the 2.0 mg/mL dose that was previously evaluated for these products.

6.6. Multicenter Considerations

Because the study will be performed at only one site, the University of Maryland Center for Vaccine Development, no multicenter considerations will be made.

6.7. Multiple Comparisons/Multiplicity

Multiplicity adjustments are not planned.

7. STUDY SUBJECTS

7.1. Subject Disposition

A subject disposition table (Table 1.3) will summarize overall and group-level disposition information. The table will provide the percentage of the initial group and overall population that participated for each visit period, along with completion of the screener, randomization, and immunizations. Furthermore, a detailed list of all study withdrawals (reasons for withdrawal and time of withdrawal) will be provided in Listing 1.3.

7.2. Protocol Deviations

All subject-specific deviations from the protocol (e.g., failure to return for follow-up visits or blood collection within the time indicated in the protocol) are to be documented, and presented as Listing 1.2 and Table 1.4. The PI or designee will be responsible for identifying and reporting all deviations, which are defined as isolated occurrences involving a procedure that did not follow the study protocol or study-specific procedure. Deviations will be reported annually in the continuing review report to the UMB IRB and/or the ORP and, if appropriate, in the final study report. Action taken in response to the deviation, and the impact of the deviation will be assessed by the PI or subinvestigator and recorded as significant or nonsignificant.

Any protocol deviation that adversely affects the safety or rights of a subject or scientific integrity of the study, the deviation will be reported immediately to the sponsor's representative, UMB IRB and/or the ORP.

8. SAFETY EVALUATION

Safety analysis will include data collected from the Safety Population. Adverse event data will be listed individually (including intervention and outcome) (Listings 1.11.1, 1.11.2, and 1.11.3) and summarized by body system and preferred terms within a body system for each treatment group. Serious and/or unexpected AEs will also be discussed on a case-by-case basis. For the tabulation of the AEs by body system, 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 AEs within the class. Therefore the total number of AEs reported within a body system may exceed the number of subjects within the body system reporting AEs. Tables 4.1 and 4.2 will present data about which groups ever experienced adverse effects.

8.1. Safety Review Committee (SRC)

The SRC will be composed of:

- PI and/or subinvestigator
- Research monitor (RM)/Independent Safety Monitor (ISM)
- DMID Medical Monitor
- USAMMDA pharmacovigilance physician or designee

Objective pre-defined halting rules and safety evaluations will be utilized. For sentinel subjects, the SRC will evaluate safety data at 48 hours post first dose. If none of the pre-defined halting rules are observed in the sentinel subjects, vaccination of the remainder of the cohorts will proceed. Should any of the study halting rules be met, the PI will notify ORA PSSB within 24 hours. The SMC will meet to evaluate data and make a recommendation regarding the trial. The SMC recommendation will be documented and provided in writing to the ORA PSSB. The sponsor's representative will then decide to terminate, modify, or continue the conduct of the study. The ORA PSSB will communicate the final decision to the appropriate parties involved in the study (ie, PI, RM/ISM, and DMID). The PI will in turn notify the IRB as appropriate. USAMRMC RA Scientist will communicate the final decision to FDA as appropriate.

8.2. Demographic and Other Baseline Characteristics

Demographic descriptive statistics will be presented in tabular form (Table 1.5). The table will report frequencies of categorical demographic variables such as subject race, ethnicity (Hispanic or Latino / Not Hispanic or Latino), and sex, whereas mean, median, standard deviation, first quartile, third quartile, minimum, and maximum values will be reported for age. These summaries will be reported overall for all study participants and by treatment group. Subjects may choose to identify as more than one race, or refuse to identify altogether. For sex, subjects may choose to report as male, female, or intersex.

All demographics, concomitant medical conditions, concomitant medications, and vital signs will be provided on an individual basis in list form (Listing 1.4) in the Appendix.

8.3. Concomitant Illnesses and Medical Conditions

Concomitant illnesses and medical conditions will be recorded prior to the study and during each injection visit. Listing 1.5 will report the prevalence of concomitant illness treatment group, subject ID, condition start/end day, whether it is a pre-existing condition, if the participant is taking medication for it, and, if yes, and the concomitant medication number. Physical exam findings will also be listed in Listing 1.9. Table 1.6 will present a summary of subjects with pre-existing medical conditions.

8.3.1. Prior and Concomitant Medications

Concomitant medications will be recorded prior to the study and during each injection visit. Listing 1.6 will report all concomitant medication by time of use, type of medication, and subject group.

8.4. Measurements of Treatment Compliance

Subjects who are unable to follow the study requirements and arrive at study visits will be withdrawn from the study at the PI's discretion. Poor compliance with study visits would include the inability to come to a scheduled study visit within the proper window on 2 or more occasions. Compliance prevalence by treatment group at each study visit period will be included in the subject disposition table (Table 1.3), and Table 1.7 Visit Completion Rates by Treatment Group.

8.5. Adverse Events

The safety evaluation will center on the nature, frequency, and severity of adverse events (AEs) and/or serious adverse events (SAEs) associated with TDS-EP-based administration of HTNV and PUUV DNA vaccines.

ICH E6 Good Clinical Practice Guidelines define an adverse event (AE) as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product regardless of its causal relationship to the study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product.

An AE is considered to be any adverse change or exacerbation from a baseline condition that occurs following the initial administration of an investigational product whether or not the event is considered to be related to the investigational product. Examples of this include but are not limited to the following:

- Adverse changes including new signs and symptoms, intercurrent illness modifying the clinical course, or the worsening of a baseline condition including the increased frequency of an event or an increased intensity of a condition
- Concomitant disease with onset or increased severity after the start of study product administration

- A new pattern in a preexisting condition, occurring after the receipt of investigational product that may signal a clinically meaningful change
- Clinically significant changes in laboratory values

Adverse events will be classified by MedDRA® System Organ Class and Preferred Term, severity, and relationship to study treatment. AEs will be documented in terms of a medical diagnosis. When this is not possible, the adverse event will be documented in terms of signs and/or symptoms observed by the investigator or reported by the subject at each study visit. AEs occurring while on study will be documented appropriately regardless of relationship.

Any hospitalization will be considered a serious adverse event. Information to be collected include event description, date of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and date of resolution/stabilization of the event. All AEs will be followed to adequate resolution or stabilization.

A complete listing of adverse events for each subject will provide details including severity, relationship to study product, onset, duration, and outcome. Laboratory results will be summarized by laboratory parameter, severity, study day, and study group. Figures 1.3 and 1.4 will present details of adverse effects, by group and visit number. Tables 2.1 to 2.3.4 present data about adverse effects.

8.5.1. Relationship to Investigational Product

The investigator must assign a relationship of each AE to the receipt of the investigational product. The investigator will use clinical judgment in conjunction with the assessment of a plausible biologic mechanism, a temporal relationship between the onset of the event in relation to receipt of the investigational product, and identification of possible alternate etiologies including underlying disease, concurrent illness or concomitant medications. The following guidelines should be used by investigators to assess the relationship of an AE to study product administration. **ONLY A PHYSICIAN CAN MAKE THIS DETERMINATION.**

- Not related: No relationship to investigational product. Applies to those events for which evidence exists that there is an alternate etiology.
- Unlikely: Likely unrelated to the investigational product. Likely to be related to factors other than the investigational product, but cannot be ruled out with certainty.
- Possible: An association between the event and the administration of investigational product cannot be ruled out. There is a reasonable temporal association, but there may also be an alternative etiology, such as the subject's clinical status or underlying factors (including other therapy).
- Probable: There is a high degree of certainty that a relationship to the investigational product exists. There is a reasonable temporal association, and the event cannot be explained by known characteristics of the subject's clinical state or factors including other therapy.
- Definite: An association exists between the receipt of investigational product and the event. An association to other factors has been ruled out.

The sponsor uses five categories of relatedness (defined above), which are to be used for this clinical trial. DMID uses only two categories of relatedness: "Not Related" and "Related". The Sponsor's category of "Not Related" maps to DMID category of "Not Related", while the Sponsor's categories of "Unlikely", "Possible", "Probable" and "Definite" map to the DMID category of "Related".

8.5.2. Severity Assessment

All 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 assigned one of the following categories: mild, moderate, or severe. Refer to the grading scale in Protocol Appendix C for further guidance in the assignment of severity. The criteria below may be used for any symptom not included in the grading scale. Any potentially life threatening/life threatening or fatal AE must be reported as an SAE.

The eCRF for AEs will reflect only the highest severity for continuous days an event occurred.

Mild	Grade 1	Does not interfere with routine activities; minimal level of discomfort
Moderate	Grade 2	Interferes with routine activities; moderate level of discomfort
Severe	Grade 3	Unable to perform routine activities; significant level of discomfort
Potentially life threatening	Grade 4	Hospitalization or ER visit for potentially life-threatening event
Fatal	Grade 5	Death

FDA guidelines for toxicity will be followed; however, if a subject is evaluated in an emergency room for nonlife threatening illness or symptoms (i.e., visits emergency department on weekend for mild problems because the physician's office is closed), the information from that visit will be reviewed and severity of the adverse event will be assessed according to the subject's clinical signs and symptoms.

As defined by the ICH guideline for GCP, the term "severe" is often used to describe intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself however, may be of relatively minor medical significance (such as severe headache). This is **not** the same as "serious", which is based on subject/event **outcome** or **action** criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

8.5.3. Solicited Events and Symptoms

A solicited AE is a predetermined event, identified in the Investigator's Brochure, which may reflect safety concerns related to the investigational product. The solicited AEs for this study include:

- Redness, swelling, bruising, pain or tenderness at the injection site
- Fever
- Myalgia (general muscle aches)
- Headache
- Lymphadenopathy
- Axillary pain or discomfort
- Tachypnea
- Fatigue

The study analysis will include Solicited AEs occurring from the time of each injection through 14 days following each procedure. Tables 2.3.1 and 2.3.2 will summarize Solicited AEs by the number and percentage of subjects experiencing solicited events by symptom, relationship to study product, treatment group, and maximum severity.

All reported solicited AEs will be provided in Listing 1.11.3.

8.5.4. Unexpected Adverse Events or Unexpected Suspected Adverse Reaction

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

8.5.5. Unanticipated Problems Involving Risks to Subjects or Others

Federal regulations require that unanticipated problems involving risks to subjects or others be promptly reported to the IRB. These events encompass a broader category of events than SAEs and may include issues such as problems with loss of control of subject data or the investigational product; adverse psychological reactions; or breach of confidentiality. Risks to others (eg, program personnel) must also be reported.

Unanticipated problems involving risks to subjects or others are any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the procedures that are described in the protocol, investigators brochure or informed consent document; and (b) the characteristics of the subject population;
- Related or possibly related to a subject's participation in the study; and
- Suggests that the study places subjects or others at a greater risk of harm than was previously known or recognized.

The PI will determine whether a given incident, experience or outcome constitutes an unanticipated problem involving risk to subjects or others and, in coordination with the sponsor, ensure upward reporting of the unanticipated problems involving risk to subjects or others to the appropriate regulatory offices.

Tables 2.3.3 and 2.3.4 will be created to summarize the incidence and intensity of solicited AEs. The tables will provide the number and percentage of subjects experiencing unexpected adverse events considered unrelated, unlikely, possibly, probably, or definitely related; as well as by MedDRA® System Organ Class, Severity, and Treatment Group.

All reported unexpected AEs or Unexpected Suspected Adverse Reactions will be provided in Listing 1.11.2.

8.6. Serious Adverse Event or Serious Suspected Adverse Reaction

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect

An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

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 subject 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, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All SAEs will be:

- Assessed for severity and relationship to study product and alternate etiology (if not related to study product) by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator Day 1 through Day 220.
- Recorded on the appropriate SAE form and eCRF.
- Followed through resolution or stabilization by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.
- Reviewed and evaluated by an SMC, RM/ISM, DMID, PSSB PVG physician, and the IRB, if indicated

All reported SAEs will be provided in Listing 1.11.1, which will include treatment group, subject ID, date reported, dose number, body system, MedDRA preferred term, severity grade, intervention, outcome, relationship to study product, and, if not, the etiology.

8.7. Pregnancies

Each pregnancy must be reported immediately (within 24 hours of identification) by email or fax to the USAMRMC ORA PSSB. Report the incident to UMB IRB and/or the USAMRMC ORP in accordance with IRB policy.

Subjects who become pregnant after Day 0 will be followed until 30 days after delivery to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. The following information will be gathered for outcome, date of delivery, health status of the mother and child including the child's gender, height and weight. Complications and or abnormalities should be reported including any premature terminations. A pregnancy is reported as an AE or SAE only when there is suspicion that the investigational product may have interfered with the effectiveness of contraception or there was a serious complication in the pregnancy including a spontaneous abortion or an elective termination for medical rationale, or the infant has a congenital anomaly/birth defect.

8.8. Clinical Laboratory Evaluations

Clinical Safety Laboratory testing will be performed at the following study visits: Screens, 1, 3, 4, 6, 7 and 9. (Listing 1.7)

For hematology and serum chemistry tests, any clinically significant changes from baseline value will be identified and reported.

The median, interquartile range, and normal values for each laboratory values (as determined by the contract laboratory) will be reported for each treatment group for each specimen collection point.

8.9. Vital Signs and Physical Evaluations

Vital sign measurements will be collected at each of the 12 study visits (Listing 1.8). Full or directed Physical Examinations will be performed at each of the 12 study visits (Listing 1.9).

8.10. Concomitant Medications

The only restrictions on the use of concomitant medications by subjects during this study are medications that are presented in protocol section 9.3. Concomitant medication use will be assessed at each study visit and provided in Listing 1.6.

9. IMMUNOGENICITY

Descriptive analysis of immunogenicity outcomes will include all subjects who meet the eligibility criteria, received at least one vaccination, and for whom serological data is available. The primary analysis variable is the proportion of seropositive subjects (PsVNA50 ≥ 1:20) at each scheduled time point (e.g., Days 0, 28, 56, 84, 140, and 220) (Table 3.1), and the final overall rate of seroconversion over these timepoints. Additionally, the proportion of subjects to ever reach seropositivity will be provided at each scheduled time point for which blood samples are taken (Table 3.2). Duration of seropositivity is presented in Table 3.3.For each study group, a binomial proportion, and corresponding 95% CI will be calculated. Chi-squared test or Fisher's exact test will be used to examine the association between group and each binary outcome of interest. Figures 1.1 and 1.2 will present percentages of subjects with seropositivity and seroconversion, by time point by group.

The secondary analysis variable is geometric mean titers, with 95% CIs, of the PsVNA50 for HTNV and PUUV specific antibodies at each scheduled time point (e.g., Days 0, 28, 56, 84, 140, and 220), and will be presented in Figure 1.5. Geometric mean titers, standard errors, and 95% CIs will be calculated using log-transformed titers, titers below the lower limit of detection (<20) will be transformed to a value equal to the lower limit of detection divided by the square root of 2 ($20/\sqrt{2}$) = 14.1 Hornung & Reed (1990) (Table 3.4). PsVNA80 titers may be calculated from existing data for information. The reciprocal of the dilution that results in an 80% decrease in luciferase activity is the PsVNA80 titer. PsVNA using other hantavirus PsV (eg, Seoul virus, Dobrava virus) may also be performed to evaluate levels of cross-neutralizing antibodies. Additionally, Fisher's exact test will be used to examine the difference in the proportion of participants to ever seroconvert between each two groups (Table 4.3).

10. REPORTING CONVENTIONS

Means, medians, standard deviations, first quartile, third quartile and range values will be rounded to less decimal places than Stata output to the extent that informational integrity is unharmed. Proportions will be reported to two decimal places.

11. TECHNICAL DETAILS

Stata version 14 will be used for all data management, analysis, and figure creation. To produce tables, data will be exported into Word/Excel.

12. REFERENCES

Richard W. Hornung & Laurence D. Reed (1990) Estimation of Average Concentration in the Presence of Nondetectable Values, Applied Occupational and Environmental Hygiene, 5:1, 46-51, DOI: 10.1080/1047322X.1990.10389587

APPENDIX I: TABLE MOCK-UPS

Appendix I: Table Mock-Ups

A Phase 1, Randomized Trial to Assess the Safety, Reactogenicity, and Immunogenicity of a Combination HTNV and PUUV DNA Vaccine Candidate Administered by Electroporation

Statistical Analysis Plan

Version 2.0

April 16, 2018

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TABLE 1.1: Ineligibility Summary of Screen Failures

	Criterion	Frequency*
Inclusion	Any inclusion criterion	
	[inclusion criterion 1]	
	[inclusion criterion 2]	
	[inclusion criterion 3]	
Exclusion	Any exclusion criterion	
	[exclusion criterion 1]	
	[exclusion criterion 2]	
	[exclusion criterion 3]	
		Total:

*More than one criterion may be marked per subject

TABLE 1.2: Analysis Population by Treatment Group

Analysis Population	Reason Subjects Excluded	Group 1 (N=X)		Group 2 (N=X)		Group 3 (N=X)		Group 4 (N=X)		Group 5 (N=X)		Group 6 (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%
Safety Population	Any Reason														
	[Reason 1, for example: Did not meet eligibility criteria]														
	[Reason 2]														
	[Reason 3]														
Immunogenicity Population	Any Reason														
	[Reason 1]														
	[Reason 2]														

*More than one criterion may be marked per subject

TABLE 1.3: Subject Disposition by Treatment Group

Subject Completed:	Group 1 (N=X)		Group 2 (N=X)		Group 3 (N=X)		Group 4 (N=X)		Group 5 (N=X)		Group 6 (N=X)		All Subjects (N=X)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Screened[a]	--	--	--	--	--	--	--	--	--	--	--	--		
Enrolled/Randomized														
Immunization 1														
Immunization 2														
Immunization 3														
All Immunizations														
Visit 1[b]														
Visit 2														
Visit 3														
Visit 4														
Visit 5														
Visit 6														
Visit 7														
Visit 8														
Visit 9														
Visit 10														
Visit 11														
Visit 12														

a) Subjects not assigned to groups at screening stage
b) Visit completion requires compliance for all scheduled tasks at each visit.

TABLE 1.4: Distribution of Protocol Deviations by Category, Type, and Treatment Group

Category	Deviation Type:	Group 1 (N=X)		Group 2 (N=X)		Group 3 (N=X)		Group 4 (N=X)		Group 5 (N=X)		Group 6 (N=X)		All Subjects (N=X)	
		# of Subj.	# of Dev.	# of Subj.	# of Dev.	# of Subj.	# of Dev.	# of Subj.	# of Dev.	# of Subj.	# of Dev.	# of Subj.	# of Dev.	# of Subj.	# of Dev.
Treatment administration schedule	Any type														
	Out of window visit														
	Missed visit/visit not conducted														
	Missed treatment administration														
	Delayed treatment administration														
	Other														
Follow-up visit schedule	Any type														
	Out of window visit														
	Missed visit/visit not conducted														
	Other														
Protocol procedure/assessment	Any type														
	Incorrect version of ICF signed														
	Blood not collected														
	Urine not collected														
	Other specimen not collected														
	Too few aliquots obtained														
	Specimen result not obtained														
	Required procedure not conducted														
	Required procedure done incorrectly														
	Study product temperature excursion														
	Specimen temperature excursion														
	Other														
Treatment administration	Any type														
	Required procedure done incorrectly														
	Study product temperature excursion														
	Other														

TABLE 1.5: Summary of Demographic and Baseline Characteristics by Treatment Group

		Group 1 (N=X)	Group 2 (N=X)	Group 3 (N=X)	Group 4 (N=X)	Group 5 (N=X)	Group 6 (N=X)	All Subjects (N=X)
Sex – n(%)	Male	x (xx)	x (xx)					
	Female							
	Intersex							
Ethnicity – n(%)	Not Hispanic or Latino	x (xx)	x (xx)					
	Hispanic or Latino							
	Not Reported							
	Unknown							
Race – n(%)	American Indian or Alaska Native	x (xx)	x (xx)					
	Asian							
	Native Hawaiian or Other Pacific Islander							
	Black or African American							
	White							
	Multi-Racial							
	Unknown							
Age	Mean	x.x	x.x					
	Standard Deviation							
	1st Quartile							
	Median							
	3rd Quartile							
	Minimum							
	Maximum							

TABLE 1.6: Summary of Subjects with Pre-Existing Medical Conditions by MedDRA® System Organ Class and Treatment Group

MedDRA® System Organ Class	Group 1 (N=X)		Group 2 (N=X)		Group 3 (N=X)		Group 4 (N=X)		Group 5 (N=X)		Group 6 (N=X)		All Subjects (N=X)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Any SOC														
[SOC 1]														
[SOC 2]														
[SOC 3]														

Note: A subject is only counted once per SOC.

TABLE 1.7: Visit Completion Rates by Treatment Group

	Group 1 (N=X)	Group 2 (N=X)	Group 3 (N=X)	Group 4 (N=X)	Group 5 (N=X)	Group 6 (N=X)
# participants enrolled with scheduled visits						
# participants missing ≥ 1 visit						
% participants missing ≥ 1 visit						
# expected scheduled visits						
# total scheduled visits						
# missed visits						
% scheduled visits completed						

TABLE 2.1: Injection Pain, Efficiency, and Speed by Treatment Group

		Group 1 All Injections (N=X)	Group 2 All Injections (N=X)	Group 3 All Injections (N=X)	Group 4 All Injections (N=X)	Group 5 All Injections (N=X)	Group 6 All Injections (N=X)	All Subjects All Injections (N=X)
Volunteer pain assessment – n (%)	1 - Painless	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
	2 - Mild pain	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
	3 - Moderate pain	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
	4 - Severe pain	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
Total number of needle sticks – n (%)	1	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
	2	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
	3	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
	4 or more sticks	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
Total number of syringes[a] – n (%)	1	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
	2	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
If ONLY 1 stick injection was required, how would you rate the procedure? – n (%)	Simple	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
	Moderately difficult	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
	Very difficult	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
Minutes between Thawing to Syringe hand-off	n	x	x	x	x	x	x	x
	Mean (SD)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)
	Median [Q1, Q3]	x [x,x]	x [x,x]	x [x,x]	x [x,x]	x [x,x]	x [x,x]	x [x,x]
	(Min, Max)	(x,x)	(x,x)	(x,x)	(x,x)	(x,x)	(x,x)	(x,x)
Minutes between Syringe hand-off to Injection Completion	n	x	x	x	x	x	x	x
	Mean (SD)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)
	Median [Q1, Q3]	x [x,x]	x [x,x]	x [x,x]	x [x,x]	x [x,x]	x [x,x]	x [x,x]
	(Min, Max)	(x,x)	(x,x)	(x,x)	(x,x)	(x,x)	(x,x)	(x,x)

[a]If more than one syringe was used, data from the last syringe is included in this table.

Q1: first quartile; Q3: third quartile.

TABLE 2.2: Global Summary of Adverse Events

Number of Participants Immunized= N	All Adverse Events	Possibly, Probably or Definitely Related Adverse Events
Subjects with at least one solicited AE by 16 days of immunization [n (%)]	x (xx)	x (xx)
Total # solicited AEs [n (maximum severity grade)]	x (Grade X)	x (Grade X)
Subjects with a solicited Grade 3 AE [n (%)]	x (xx)	x (xx)
Subjects with at least one solicited local AE	x (xx)	x (xx)
Total # local AEs	x (Grade X)	x (Grade X)
Average # local AEs/volunteers experiencing local AEs	x.xx	x.xx
Subjects with at least one solicited systemic AE	x (xx)	x (xx)
Total # systemic AEs	x (Grade X)	x (Grade X)
Average # systemic AEs/volunteers experiencing systemic AEs	x.xx	x.xx
Subjects with at least one unsolicited AE within 32 days of immunization [n (%)]	x (xx)	x (xx)
Total # unsolicited AEs within 32 days of immunization [n (maximum severity grade)]	x (Grade X)	x (Grade X)
Subjects with an unsolicited Grade 3 AE [n (%)]	x (xx)	x (xx)
Subjects experiencing an SAE[a] [n (%)]	x (xx)	x (xx)
Total # of SAEs [n (maximum severity grade)]	x (Grade X)	x (Grade X)

a) An adverse event or suspected adverse reaction is considered "serious" (SAE) if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect

TABLE 2.3.1: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Relationship to Study Product, and Treatment Group

NOTE: Table will be repeated for each injection dose

Symptom	Relationship to Study Product	Group 1 (N=X)		Group 2 (N=X)		Group 3 (N=X)		Group 4 (N=X)		Group 5 (N=X)		Group 6 (N=X)	
		n	%	n	%	n	%	n	%	n	%	n	%
Any Symptom	Related												
	Unrelated												
Redness, swelling, bruising, or pain (to include tenderness) at the injection site	Related												
	Unrelated												
Fever	Related												
	Unrelated												
Myalgia	Related												
	Unrelated												
Headache	Related												
	Unrelated												
Lymphadenopathy	Related												
	Unrelated												
Axillary pain or discomfort	Related												
	Unrelated												
Tachypnea	Related												
	Unrelated												
Fatigue	Related												
	Unrelated												

TABLE 2.3.2: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity, and Treatment Group

NOTE: Table will be repeated for each injection dose

Symptom	Severity Grade	Group 1 (N=X)		Group 2 (N=X)		Group 3 (N=X)		Group 4 (N=X)		Group 5 (N=X)		Group 6 (N=X)	
		n	%	n	%	n	%	n	%	n	%	n	%
Any Symptom	None												
	1												
	2												
	3												
	Any												
Redness, swelling, bruising, or pain (to include tenderness) at the injection site	None												
	1												
	2												
	3												
	Any												
Fever	None												
	1												
	2												
	3												
	Any												
Myalgia	None												
	1												
	2												
	3												
	Any												

Symptom	Severity Grade	Group 1 (N=X)		Group 2 (N=X)		Group 3 (N=X)		Group 4 (N=X)		Group 5 (N=X)		Group 6 (N=X)	
		n	%	n	%	n	%	n	%	n	%	n	%
Headache	None												
	1												
	2												
	3												
	Any												
Lymphadenopathy	None												
	1												
	2												
	3												
	Any												
Axillary pain or discomfort	None												
	1												
	2												
	3												
	Any												
Tachypnea	None												
	1												
	2												
	3												
	Any												
Fatigue	None												
	1												
	2												
	3												
	Any												

TABLE 2.3.3: Number and Percentage of Subjects Experiencing Unexpected Adverse Events or Unexpected Suspected Adverse Reaction Considered Possibly, Probably, or Definitely Related by MedDRA® System Organ Class, Severity, and Treatment Group

Symptom	Severity Grade	Group 1 (N=X) n	%	Group 2 (N=X) n	%	Group 3 (N=X) n	%	Group 4 (N=X) n	%	Group 5 (N=X) n	%	Group 6 (N=X) n	%
FIRST DOSE:													
Any SOC	1												
	2												
	3												
	Any												
[SOC 1]	1												
	2												
	3												
	Any												
[SOC 2]	1												
	2												
	3												
	Any												
SECOND DOSE:													
Any SOC	1												
	2												
	3												
	Any												
[SOC 1]	1												
	2												
	3												
	Any												
[SOC 2]	1												
	2												
	3												
	Any												
THIRD DOSE:													
Any SOC	1												
	2												
	3												

Symptom	Severity Grade	Group 1 (N=X) n	%	Group 2 (N=X) n	%	Group 3 (N=X) n	%	Group 4 (N=X) n	%	Group 5 (N=X) n	%	Group 6 (N=X) n	%
	Any												
[SOC 1]	1												
	2												
	3												
	Any												
[SOC 2]	1												
	2												
	3												
	Any												

TABLE 2.3.4: Number and Percentage of Subjects Experiencing Unexpected Adverse Events or Unexpected Suspected Adverse Reaction Considered Unrelated or Unlikely Related by MedDRA® System Organ Class, Severity, and Treatment Group

Table follows Table 2.3.3 formatting.

TABLE 3.1: Proportion of Seropositive Subjects at Each Blood Collection Time Point

	Group 1 (N=X)		Group 2 (N=X)		Group 3 (N=X)		Group 4 (N=X)		Group 5 (N=X)		Group 6 (N=X)	
Collection Point	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
1	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	[x,x]		[x,x]		[x,x]		[x,x]		[x,x]		[x,x]	
2												
3												
4												
5												
6												
7												

Note: 95% confidence intervals for sample proportion in brackets

TABLE 3.2: Proportion of Subjects that Ever Seroconverted at Each Blood Collection Time Point

	Group 1 (N=X)		Group 2 (N=X)		Group 3 (N=X)		Group 4 (N=X)		Group 5 (N=X)		Group 6 (N=X)	
Collection Point	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
1	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	[x,x]		[x,x]		[x,x]		[x,x]		[x,x]		[x,x]	
2												
3												
4												
5												
6												
7												

Note: 95% confidence intervals for sample proportion in brackets

TABLE 3.3: Duration of Seropositivitiy if Ever Seroconverted

	Group 1 (n=x)	Group 2 (n=x)	Group 3 (n=x)	Group 4 (n=x)	Group 5 (n=x)	Group 6 (n=x)
Mean						
Standard Deviation						
95% CI for Mean						
1st Quartile						
Median						
3rd Quartile						
Min						
Max						

TABLE 3.4: Geometric Mean Titers of the PsVNA50 at Each Blood Collection Time Point

	Group 1 (N=X)		Group 2 (N=X)		Group 3 (N=X)		Group 4 (N=X)		Group 5 (N=X)		Group 6 (N=X)	
Collection Point	**μ**	**SD**	**μ**	**SD**	**μ**	**SD**	**μ**	**SD**	**μ**	**SD**	**μ**	**SD**
1	x	x	x	x	x	x	x	x	x	x	x	x
	[x,x]		[x,x]		[x,x]		[x,x]		[x,x]		[x,x]	
2												
3												
4												
5												
6												
7												

Note:

- μ = mean; SD = standard deviation
- 95% confidence intervals for sample proportion in brackets

TABLE 4.1: Safety Analysis Group Comparison: Ever Experienced Solicited Adverse Events

Group:	1	2	3	4	5	6	P-value[1]
N=	x	x	x	x	x	x	
% Reporting	xx	xx	xx	xx	xx	xx	x
(95% CI)	(x,x)	(x,x)	(x,x)	(x,x)	(x,x)	(x,x)	
Pair 1	•	•					x
Pair 2			•	•			x
Pair 3					•	•	x
Pair 4	•				•		x
Pair 5			•		•		x
Pair 6		•				•	x
Pair 7				•		•	x

[1]P-value obtained from a two-sided Fisher's exact test

TABLE 4.2: Safety Analysis Group Comparison: Ever Experienced Unsolicited Adverse Events

Group:	1	2	3	4	5	6	P-value[1]
N=	x	x	x	x	x	x	
% Reporting (95% CI)	xx (x,x)	xx (x,x)	xx (x,x)	xx (x,x)	xx (x,x)	xx (x,x)	x
Pair 1	•	•					x
Pair 2			•	•			x
Pair 3					•	•	x
Pair 4	•				•		x
Pair 5			•		•		x
Pair 6		•				•	x
Pair 7				•		•	x

[1]P-value obtained from a two-sided Fisher's exact test

TABLE 4.3: Immunogenicity Analysis: Ever Seroconverted

Group:	1	2	3	4	5	6	P-value[1]
N=	x	x	x	x	x	x	
% Reporting	xx	xx	xx	xx	xx	xx	x
(95% CI)	(x,x)	(x,x)	(x,x)	(x,x)	(x,x)	(x,x)	
Pair 1	•	•					x
Pair 2			•	•			x
Pair 3					•	•	x
Pair 4	•				•		x
Pair 5			•		•		x
Pair 6		•				•	x
Pair 7				•		•	x

[1]P-value obtained from a two-sided Fisher's exact test

APPENDIX II: FIGURE MOCK-UPS

Appendix II: Figure Mock-Ups

A Phase 1, Randomized Trial to Assess the Safety, Reactogenicity, and Immunogenicity of a Combination HTNV and PUUV DNA Vaccine Candidate Administered by Electroporation

Statistical Analysis Plan

Version 2.0

April 16, 2018

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FIGURE 1.1: Percentage of Subjects Seropositive at Each Blood Collection Time Point, by Group

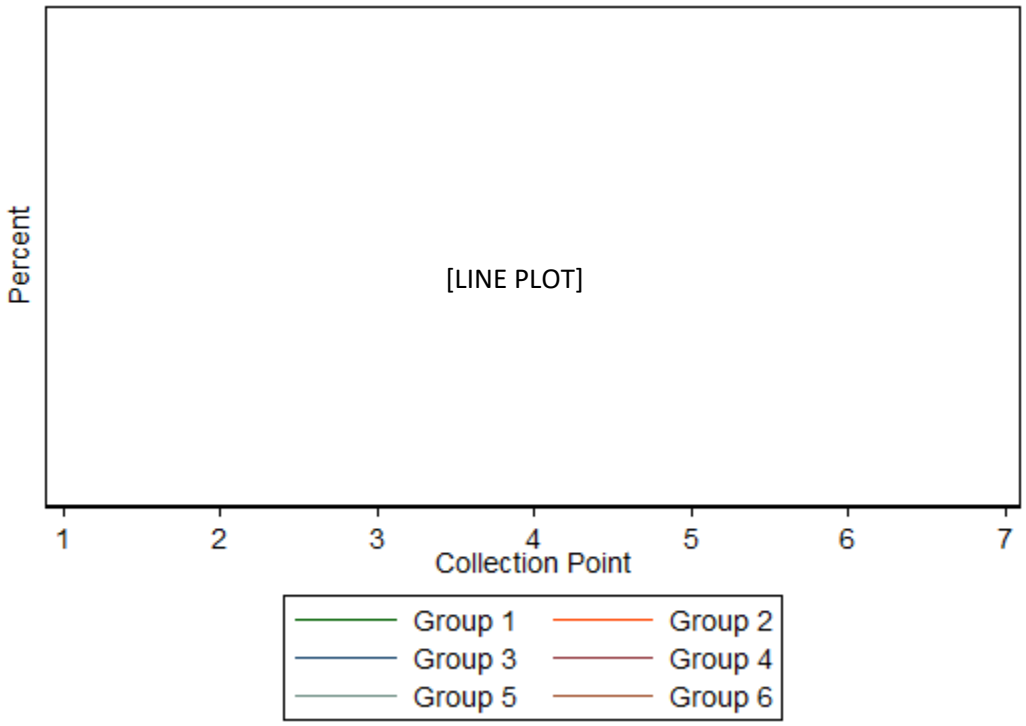


FIGURE 1.2: Percentage of Subjects that Ever Seroconverted at Each Blood Collection Time Point, by Group

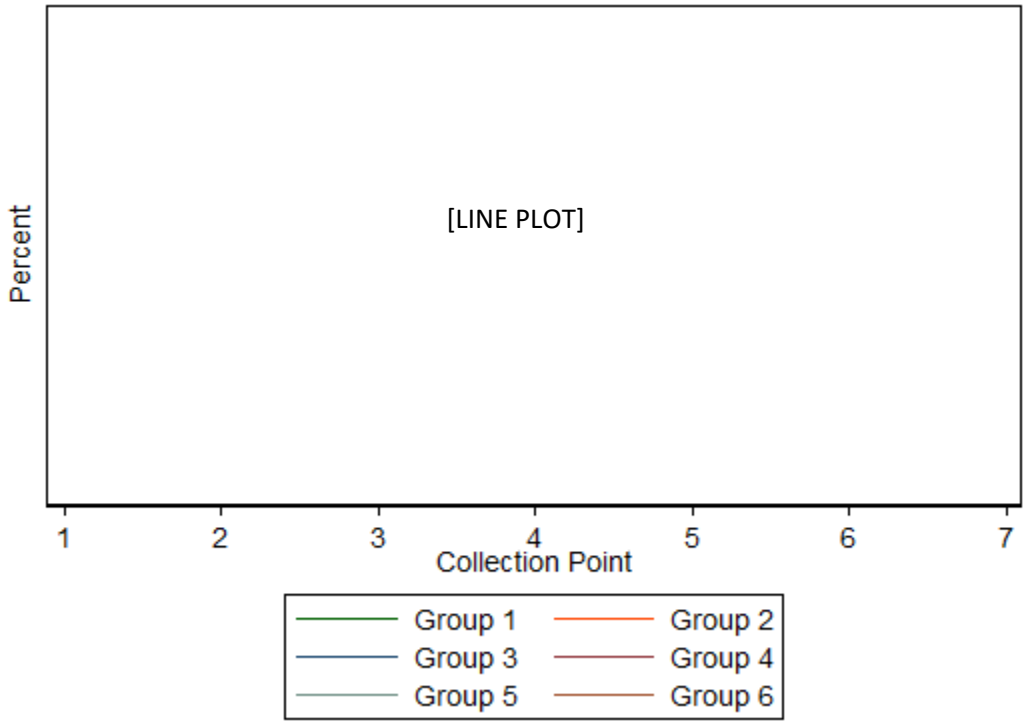


FIGURE 1.3: Percent of Participants Who Ever Reported an Adverse Effect, by Group and Visit Number

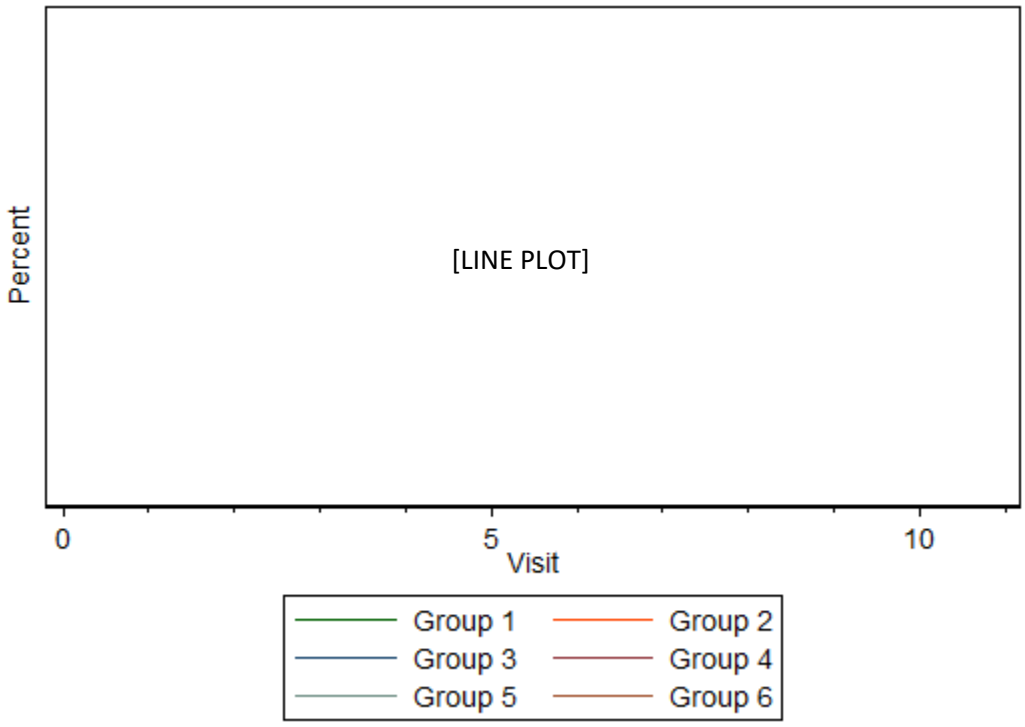


FIGURE 1.4: Percent of Participants Who Currently Reported at Least One Adverse Effect, by Group and Visit Number

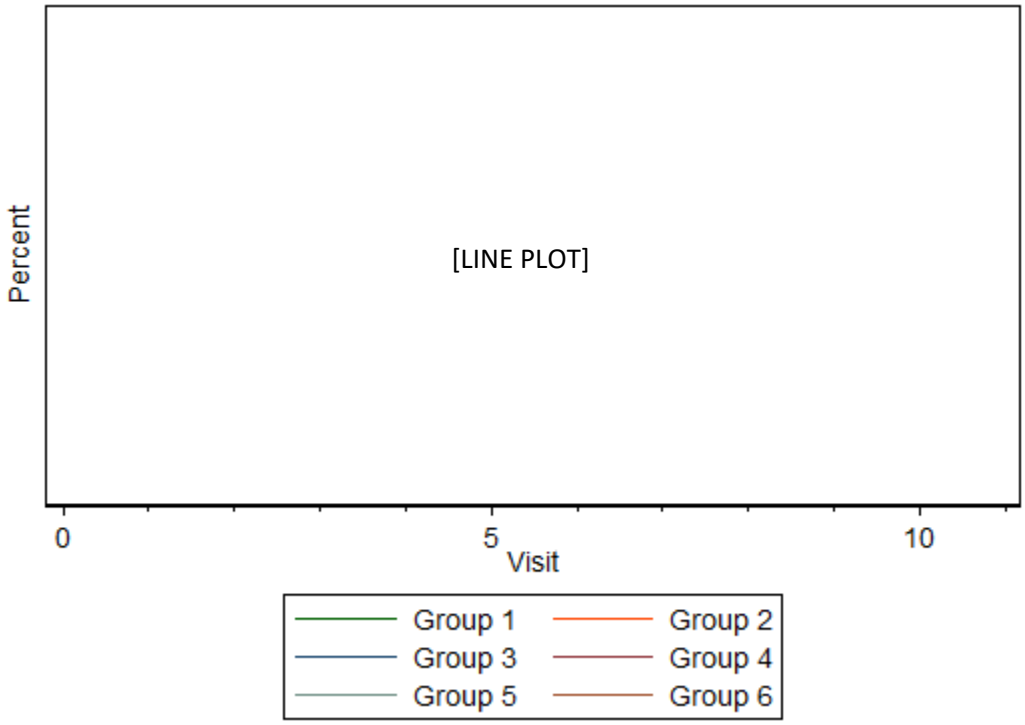
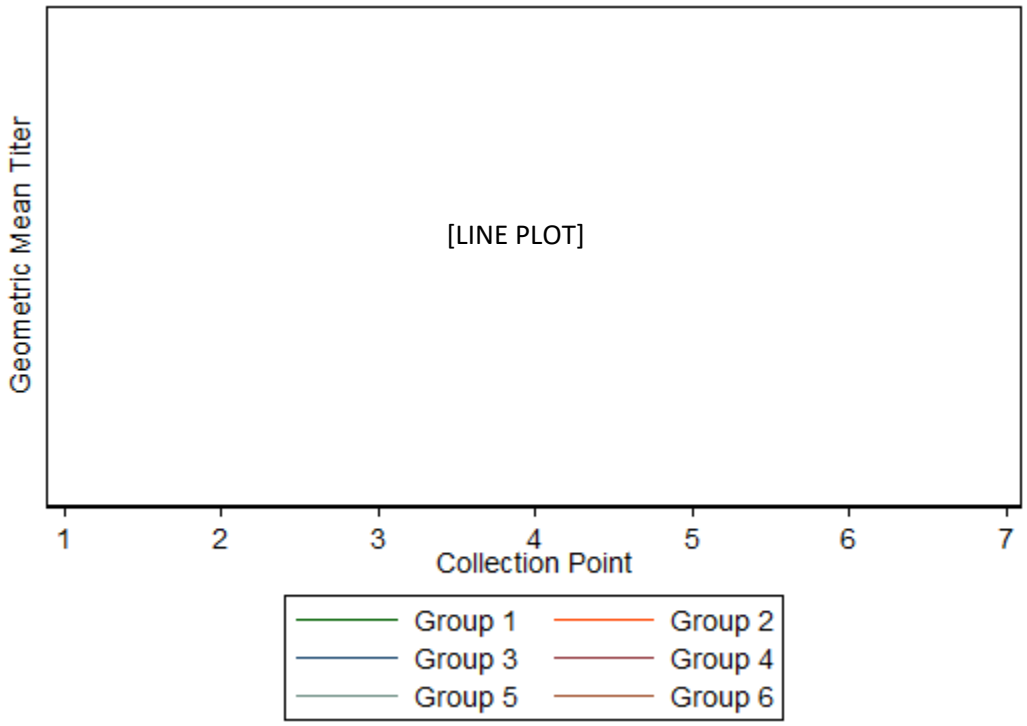


FIGURE 1.5: Geometric Mean Titers of the PsVNA50 at Each Blood Collection Time Point



APPENDIX III: LISTING MOCK-UPS

Appendix III: Listing Mock-Ups

A Phase 1, Randomized Trial to Assess the Safety, Reactogenicity, and Immunogenicity of a Combination HTNV and PUUV DNA Vaccine Candidate Administered by Electroporation

Statistical Analysis Plan

Version 3.0

January 25, 2019

Contents

LISTING 1.1: Subjects Excluded from the Study Analysis

Subject ID	Group	Date Excluded	Analysis Excluded From		Results Available?	Reason Excluded
			Safety	Immunogenicity		
		MM/DD/YYYY	x		**Yes**	
				x	**No**	
			x	**x**		

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 1.2: Protocol Deviations

Group	Subject ID	Reference Number	Date of Deviation	Deviation Description	Resolution	Resulted in AE?	Resulted in Subject Termination?	Meets IRB Reporting Req.?	IRB Reporting Date

LISTING 1.3: Study Withdraws

Group	Subject ID	Date Withdrawn	Reason Withdrawn	Followed?[a]
		MM/DD/YYYY		

a) Followed through resolution of any ongoing adverse events, per subject's permission

LISTING 1.4: Demographics

Group	Subject ID	Sex	Race	Ethnicity	Age at Enrollment

LISTING 1.5: Medical History

Treatment Group	Subject ID	MH Number	Medical History Term	Condition Start Day	Condition End Day	Pre-Existing Condition	Taking Medication For?	If yes, CM Number
						Yes		
						No		

LISTING 1.6: Concomitant Medications

Group	Subject ID	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 1.7: Clinical Laboratory Evaluations

Group	Subject ID	Planned Time Point	Actual Study Day	CBC with differential			Glucose	Cr	AST	ALT	Total Bilirubin	Viral serologies			PT/PTT
				WBC	Hb	Platelet						HBsAg	Anti-HCV Ab	Anti-HIV Ab	

LISTING 1.8: Vital Signs

Group	Subject ID	Planned Time Point	Actual Study Day	Temperature (°C)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Heart Rate (beats/min)	Respiratory Rate (breaths/min)	Weight (kg)	Height (cm)

LISTING 1.9: Physical Exam Findings

Group	Subject ID	Planned Time Point	Actual Study Day	Test	Body System	Abnormal Finding	Reported as an AE? (AE Number)

LISTING 1.10: Dose Dates by Treatment Group

Dose	Group 1 (N=X)	Group 2 (N=X)	Group 3 (N=X)	Group 4 (N=X)	Group 5 (N=X)	Group 6 (N=X)
Dose 1	DDMMMYYYY (n) DDMMMYYYY (n) […]	DDMMMYYYY (n)	DDMMMYYYY (n)	DDMMMYYYY (n) DDMMMYYYY (n)	DDMMMYYYY (n)	DDMMMYYYY (n) DDMMMYYYY (n)
Dose 2	DDMMMYYYY (n) DDMMMYYYY (n)	DDMMMYYYY (n)	DDMMMYYYY (n)	DDMMMYYYY (n)	DDMMMYYYY (n)	DDMMMYYYY (n)
Dose 3	DDMMMYYYY (n)	DDMMMYYYY (n)	DDMMMYYYY (n)	DDMMMYYYY (n)	DDMMMYYYY (n)	DDMMMYYYY (n)

Note: n = number of participants in each group dosed each day

LISTING 1.11.1: Serious Adverse Events

Group	Subject ID	Date Reported	Dose #	Body System	MedDRA Preferred Term	Severity Grade	Intervention	Outcome	Related?	If Not, Alternate Etiology
		MM/DD/YYYY								

LISTING 1.11.2: Unexpected Adverse Events or Unexpected Adverse Reactions

Group	Subject ID	Onset Date	Dose #	Body System	MedDRA Preferred Term	Severity Grade	Intervention	Outcome	Related?	If Not, Alternate Etiology
		MM/DD/YYYY								

LISTING 1.11.3: Solicited Adverse Events

Group	Subject ID	Dose #	Date Reported	Severity Grade	Redness[a]	Fever	Myalgia	Headache	Lymphadenopathy	Axillary pain or discomfort	Tachypnea	Fatigue

a) Includes swelling, bruising, or pain (to include tenderness) at the injection site