

Official Title: A Phase 1 Open Label, Dose-Escalation Clinical Trial to Evaluate the Safety and Immunogenicity of a Trivalent Virus-Like Particle (VLP) Encephalitis Vaccine, VRC-WEVVLP073-00-VP, in Healthy Adults

ClinicalTrials.gov Identifier: NCT03879603

Document Type:

- Redacted Study Protocol, including Letters of Amendment (Statistical Analysis Considerations located in Section 6 of the Protocol)
- Redacted IRB-approved Version 2.0 Informed Consent (dated March 12, 2019)

Document/Date:

- Protocol Version 1.0: January 9, 2019
- Protocol Version 1.0, Letter of Amendment #1: March 12, 2019
- Protocol Version 1.0, Letter of Amendment #2: April 23, 2019
- Protocol Version 1.0, Letter of Amendment #3: October 24, 2019
- Version 2.0 IRB-approved Informed Consent (dated March 12, 2019 with March 18, 2019 IRB-approval)

VACCINE RESEARCH CENTER

Protocol VRC 313

A PHASE 1 OPEN LABEL, DOSE-ESCALATION CLINICAL TRIAL TO EVALUATE THE SAFETY AND IMMUNOGENICITY OF A TRIVALENT VIRUS-LIKE PARTICLE (VLP) ENCEPHALITIS VACCINE, VRC-WEVVLP073-00-VP, IN HEALTHY ADULTS

Vaccine Provided by

National Institute of Allergy and Infectious Diseases (NIAID)
Vaccine Research Center (VRC)
Bethesda, Maryland

Clinical Trial Sponsored by

National Institute of Allergy and Infectious Diseases (NIAID)
Vaccine Research Center (VRC)
Bethesda, Maryland

BB-IND 11738 – held by VRC, NIAID, NIH

Clinical Trial Management

Leidos Biomedical Research, Inc.
Frederick, Maryland, USA

Protocol Chairs

Julie Ledgerwood, D.O.
Cristina A. Carter, M.D.
VRC, NIAID, NIH
Bethesda, MD 20892

Clinical Research Site Principal Investigator: Srilatha Edupuganti, MD; MPH

IRB Initial Review Date: February 20, 2019

Confidentiality Statement

This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, study staff, and applicable independent ethics committees or institutional review boards. The contents of this document shall not be disclosed to others without written authorization from NIAID (or others, as applicable), unless it is necessary to obtain informed consent from potential study subjects.

Statement of Compliance

The trial will be conducted in compliance with the protocol, the applicable regulatory requirements including but not limited to the United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR 46, 21 CFR including parts 50 and 56 concerning informed consent and Institutional Review Board (IRB)/Ethics Committee (EC) regulations, and 21 CFR 312 concerning Investigational New Drug (IND) application), International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidance, and the NIAID Clinical Terms of Contract Award. Each site will hold a current Federal Wide Assurance (FWA) issued by the Office for Human Research Protections for federally funded research. Completion of Protection of Human Subjects Training will be required for all study personnel in accordance with National Institutes of Health (NIH) policy.

PRINCIPAL INVESTIGATOR PROTOCOL SIGNATURE PAGE

VRC 313: A Phase 1 Open Label, Dose-Escalation Clinical Trial to Evaluate the Safety and Immunogenicity of a Trivalent Virus-Like Particle (VLP) Encephalitis Vaccine, VRC-WEVVLP073-00-VP, in Healthy Adults.

Sponsored by: Vaccine Research Center (VRC), National Institute of Allergy and Infectious Diseases (NIAID) National Institutes of Health (NIH)

I, the Principal Investigator for the indicated VRC 313 Study Site, agree to conduct this study in full accordance with the provisions of this protocol and protocol amendments. I will comply with all requirements regarding the obligations of investigators as outlined in the Statement of Investigator (Form FDA 1572), which I have also signed. I agree to maintain all study documentation pertaining to the conduct of this study, including, but not limited to, case report forms, source documents, consent forms, laboratory test results, and medication inventory records, for at least 2 years following submission of a United States Biologics License Application. If no marketing application is filed, or if the application is not approved, the records will be retained for two years after the investigation is discontinued and the US Food and Drug Administration is notified. No study records will be destroyed without prior authorization from VRC/NIAID. Publication of the results of this study will be governed by the VRC/NIAID policies. Any presentation, abstract, or manuscript will be made available by the investigators to VRC Leadership and to NIAID for review prior to submission.

I have read and understand the information in this protocol and the Investigator’s Brochure and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

Name/Title of Principal Investigator

Study Site Name/Identifier

Signature of Principal Investigator

Date

TABLE OF CONTENTS

TABLE OF ABBREVIATIONS	8
PRÉCIS	9
1 INTRODUCTION	10
1.1 Etiology, Epidemiology, and Disease Course	10
1.2 Rationale for the Development of the WEVEE Vaccine.....	10
1.3 Rationale for the Use of Aluminum–Based Adjuvant.....	11
1.3.1 Animal Experience with WEVEE VLP and Aluminum-based Adjuvants.....	11
1.4 Previous Human Experience.....	12
1.4.1 VRC-CHKVLP-59-00-VP (CHIK VLP) Vaccine and Other VLP Vaccines	12
1.4.2 Human Experience with Other Alphavirus Vaccines	13
1.4.3 Previous Human Experience with Aluminum-based Adjuvants	13
1.5 Rationale for Study Design.....	14
1.6 Assessment of Immunogenicity.....	14
2 STUDY PRODUCTS	14
2.1 VRC-WEVVLP073-00-VP, Study Product.....	14
2.2 VRC-GENMIX083-AL-VP, Adjuvant.....	14
2.3 VRC-PBSPLA043-00-VP, Diluent	14
2.4 Preclinical Studies of VRC-WEVVLP073-00-VP	15
3 STUDY OBJECTIVES	15
3.1 Primary Objectives	15
3.2 Secondary Objectives	15
3.3 Exploratory Objectives	15
4 STUDY DESIGN AND CLINICAL PROCEDURES	15
4.1 Study Population.....	16
4.1.1 Inclusion Criteria	16
4.1.2 Exclusion Criteria	17
4.2 Clinical Procedures And Evaluations	18
4.2.1 Pre-screening	18
4.2.2 Screening	18
4.2.3 Enrollment	19
4.2.4 Randomization.....	19
4.2.5 Study Schedule	20

4.2.6	Product Administration.....	21
4.2.7	Safety Evaluations and Follow-up after Product Administration.....	22
4.2.8	Blood Sample Collection.....	22
4.2.9	Concomitant Medications.....	22
4.3	Dose Escalation	23
4.4	Pausing and Resuming the Study	24
4.4.1	Criteria for Pausing the Study.....	24
4.4.2	Plan for Review of Pauses and Resuming the Study.....	24
4.4.3	Dose-Limiting Toxicity	24
4.5	Discontinuation of Product Administrations or Study Participation	24
4.5.1	Discontinuation of Product Administrations	24
4.5.2	Discontinuation from Protocol Participation.....	25
5	SAFETY AND ADVERSE EVENTS.....	25
5.1	Adverse Events	25
5.2	Serious Adverse Events	26
5.3	Adverse Event Reporting to the IND Sponsor	26
5.3.1	IND Sponsor Reporting to the FDA	27
5.4	Reporting to the Institutional Review Board	27
5.4.1	Unanticipated Problems.....	27
5.4.2	Protocol Deviations	28
5.4.3	Non-Compliance.....	28
5.4.4	Expedited and Annual Reporting to the site IRB	29
6	STATISTICAL CONSIDERATIONS	29
6.1	Overview.....	29
6.2	Endpoints	29
6.2.1	Primary Endpoints: Safety.....	29
6.2.2	Secondary Endpoints: Immunogenicity.....	29
6.2.3	Exploratory Endpoints: Immunogenicity	29
6.3	Sample Size and Accrual	29
6.3.1	Power Calculations for Safety	30
6.3.2	Sample Size Calculations for Immunogenicity	31
6.3.3	Power for Comparison.....	31
6.4	Statistical Analysis.....	31

6.4.1	Analysis Variables	31
6.4.2	Baseline Comparability	31
6.4.3	Safety Analysis	32
6.4.4	Immunogenicity Analysis	32
6.4.5	Missing Data	32
6.4.6	Interim Analyses of Immunogenicity	33
6.5	Randomization of Intervention Assignments	33
7	PHARMACY PREPARATION AND ADMINISTRATION PROCEDURES	33
7.1	Study Products	33
7.2	Study Product Presentation, Stability, and Storage	34
7.2.1	Labels	34
7.2.2	Stability	34
7.2.3	Storage	34
7.2.4	Deviations in Temperatures	34
7.3	Preparation of Study Product for Administration	35
7.3.1	Preparation of VRC-WEVLP073-00-VP	35
7.3.2	Preparation of VRC-WEVLP073-00-VP plus Adjuvant	36
7.4	Study Product Administration	37
7.5	Study Product Accountability	37
7.5.1	Documentation	37
7.5.2	Disposition	37
8	HUMAN SUBJECT PROTECTIONS AND ETHICAL OBLIGATIONS	37
8.1	Institutional Review Board	37
8.2	Subject Recruitment and Randomization	38
8.2.1	Participation of Children	38
8.2.2	Participation of Site Employees	38
8.3	Informed Consent	38
8.4	Subject Confidentiality	38
8.5	Risks and Benefits	39
8.5.1	Risks of the WEVEE Vaccine	39
8.5.2	Risks of Aluminum Hydroxide Suspension	39
8.5.3	Risks of Phosphate Buffered Saline	40
8.5.4	Other Risks	40

8.5.5	Benefits	40
8.6	Plan for Use and Storage of Biological Samples.....	40
8.6.1	Use of Samples, Specimens and Data.....	40
8.6.2	Storage and Tracking of Blood Samples and Other Specimens	41
8.6.3	Disposition of Samples, Specimens and Data at Completion of the Protocol.....	41
8.6.4	Loss or Destruction of Samples, Specimens or Data.....	41
8.7	Subject Compensation	41
8.8	Safety Monitoring.....	41
8.8.1	Protocol Safety Review Team	41
9	ADMINISTRATIVE AND LEGAL OBLIGATIONS	42
9.1	Protocol Amendments and Study Termination.....	42
9.2	Study Documentation and Storage	42
9.3	Data Collection and Protocol Monitoring.....	43
9.3.1	Data Collection	43
9.3.2	Data Sharing Plan	43
9.3.3	Source Documents.....	43
9.3.4	Protocol Monitoring Plan	43
9.4	Language.....	43
9.5	Policy Regarding Research-Related Injuries	44
9.6	Site Management	44
10	REFERENCES	45
	APPENDIX I: STUDY INFORMED CONSENT FORM	47
	APPENDIX II: CONTACT INFORMATION	56
	APPENDIX III: SCHEDULE OF EVALUATIONS	58
	APPENDIX IV: ASSESSMENT OF RELATIONSHIP TO VACCINE AND GRADING SEVERITY OF ADVERSE EVENTS.....	60

TABLES

Table 1:	VRC 313 Vaccination Schema	16
Table 2:	Probability of Events for Different Safety and Immunogenicity Scenarios within a Group (n=5)	30
Table 3:	95% Confidence Intervals for the True Rate At All Possible Observed Rates within a Group (n=5)	30
Table 4:	Power (%) to Detect Difference in Response Rates between Two groups by Fisher’s Exact Test, Each Group of Size n=5.....	31

TABLE OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
ALT	alanine aminotransferase
AoU	assessment of understanding
Alum	aluminum hydroxide suspension
BMI	body mass index
CBC	complete blood count
cGMP	Current Good Manufacturing Practices
EEEV	Eastern Equine Encephalitis Virus
ELISA	enzyme-linked immunosorbent assay
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GLP	Good Laboratory Practices
GMT	Geometric Mean Titer
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
IM	intramuscular
IND	investigational new drug application
IRB	Institutional Review Board
LIMS	Laboratory Information Management System
MedDRA	Medical Dictionary for Regulatory Activities
MAC-ELISA	monoclonal antibody-based antigen-capture enzyme-linked immunosorbent assay
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NHP	non-human primate
NSAID	nonsteroidal anti-inflammatory drug
PBS	phosphate buffered saline
PI	Principal Investigator
PSRT	Protocol Safety Review Team
RNA	ribonucleic acid
SAE	serious adverse event
SAS	Statistical Analysis System
SUSAR	serious and unexpected suspected adverse reaction
ULN	upper limit of normal
UP	unanticipated problem
VCMP	Vaccine Clinical Material Program
VEEV	Venezuelan Equine Encephalitis Virus
VITL	Vaccine Immunology Testing Laboratory
VLP	virus-like particles
VRC	Vaccine Research Center
WBC	white blood cell
WEEV	Western Equine Encephalitis Virus
WEVEE	Western, Eastern and Venezuelan Equine Encephalitis

PRÉCIS

VRC 313: A Phase 1 Open Label, Dose-Escalation Clinical Trial to Evaluate the Safety and Immunogenicity of a Trivalent Virus-Like Particle (VLP) Encephalitis Vaccine, VRC-WEVVLP073-00-VP, in Healthy Adults.

Study

Design: This is a Phase I, randomized, open-label, dose-escalation study to examine the dose, safety, tolerability, and immunogenicity of VRC-WEVVLP073-00-VP (WEVEE) alone or with alum adjuvant in a 2-product administration regimen. The trivalent encephalitis vaccine VRC-WEVVLP073-00-VP is composed of Western equine encephalitis (WEE), Eastern equine encephalitis (EEE), and Venezuelan equine encephalitis (VEE) VLPs. The hypotheses are that the vaccine is safe and will induce immune responses to all three alphaviruses. The primary objectives are to evaluate the safety and tolerability of the investigational vaccine at three doses administered alone or with adjuvant in healthy adults. Secondary objectives relate to immunogenicity of the investigational vaccine and dosing regimen.

Study

Product: The investigational VRC-WEVVLP073-00-VP vaccine was developed by the Vaccine Research Center (VRC) and is composed of a mixture of WEE, EEE, and VEE VLPs in a 1:1:1 mass ratio filled into single-dose vials at a concentration of 78 mcg/mL. Adjuvant is an aluminum hydroxide suspension (alum) provided in a sterile, pyrogen-free suspension at a concentration of 5 mg/mL in 3 mL glass vials filled to 0.7 ± 0.10 mL. The alum dose is 500 mcg and will be mixed during preparation of each vaccine dose. VRC-PBSPLA043-00-VP is sterile phosphate buffered saline (PBS), 1.2 mL per vial prepared for human injection as a diluent.

Subjects: Up to 40 healthy adults ages 18 to 50.

Study Plan: Eligible subjects will be randomized to receive WEVEE alone or WEVEE plus alum in each dose group. The product will be administered as an intramuscular (IM) injection in the deltoid muscle via needle and syringe on Day 0 and Week 8. For all Groups, solicited reactogenicity will be evaluated using a 7-day diary card. Assessment of vaccine safety will include clinical observation and monitoring of hematological and chemical parameters at clinical visits throughout the study. Safety dose escalation reviews will occur to ensure the safety data support proceeding to the higher doses. The study requires about 9 clinic visits and 2 telephone follow-up contacts after each product administration. The study schema is shown below.

VRC 313 Vaccination Schema				
Group	Subjects	Dose	Day 0	Week 8
1	5	6 mcg	WEVEE	WEVEE
2	5		WEVEE + alum	WEVEE + alum
3	5	30 mcg	WEVEE	WEVEE
4	5		WEVEE + alum	WEVEE + alum
5	5	60 mcg	WEVEE	WEVEE
6	5		WEVEE + alum	WEVEE + alum
Total*	30	*Up to 10 subjects over target accrual are permitted to be allocated to any group if needed for additional safety or immunogenicity evaluations.		

Study

Duration: Subjects will be evaluated for 36 weeks following the first vaccine administration.

1 INTRODUCTION

The Dale and Betty Bumpers Vaccine Research Center (VRC), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH) in Bethesda, Maryland, is dedicated to translating the latest knowledge of disease pathogenesis and immunology into new vaccine strategies to provide safe and effective means to prevent and control infectious diseases. Western Equine Encephalitis Virus (WEEV), Eastern Equine Encephalitis Virus (EEEV), and Venezuelan Equine Encephalitis Virus (VEEV) are transmitted by mosquitoes and can cause an acute infection associated with severe morbidity that can persist for several weeks, months or even years [1]. These encephalitic alphaviruses are classified as Category B bioterrorism agents by the Centers for Disease Control and Prevention (CDC) and the need to develop effective vaccines and therapeutics against these organisms is considered a high priority [2]. Alphaviruses are of significant interest for tactical weapons development (biological warfare) due to their relative stability and highly infectivity to humans in aerosol form. The viruses can be inexpensively produced in large quantities and can yield either incapacitating or lethal infections. Public health demands and preventive bioterrorism measures support the need for a safe and immunogenic vaccine. The product, VRC-WEVVLP073-00-VP (or WEVEE), is a trivalent vaccine intended to elicit broad spectrum protection against WEEV, EEEV and VEEV exposure. The study is designed as a first-in-human Phase I study to evaluate the dose, safety, tolerability and immunogenicity of the WEVEE Vaccine.

1.1 Etiology, Epidemiology, and Disease Course

WEEV, EEEV and VEEV belong to the *Alphavirus* genus of the *Togaviridae* family and have a positive sense, single-stranded ribonucleic acid (RNA) genome encoding structural and non-structural proteins. The non-structural genes include replication proteins RNA polymerase and helicase. Structural genes include the capsid, protein 6K and envelope proteins (E1, E2 and E3).

These viruses are transmitted in nature through infected mosquitoes, widely circulate in North, Central and South America, causing periodic epizootics [1]. Highly pathogenic in animals and humans, the pathology of these viruses is often associated with encephalitis and other neurological manifestations [1, 3]. Acute clinical manifestations include fever, headache, lymphopenia, myalgia and malaise. Severe neurological disease including fatal encephalitis can also occur in humans, with estimated case-fatality rates of $\leq 1\%$ for VEEV, 8-15% for WEEV, and 30-70% for EEEV [4, 5]. There is no effective antiviral treatment for any of these encephalic viruses, so treatment remains supportive [3].

Alphavirus infection can be confirmed by the isolation of nucleic acid or virus in serum or spinal fluid. The best method for virus identification is by IgM antibody-capture enzyme-linked immunosorbent assay (ELISA) using monoclonal antibody-based antigen-capture (MAC-ELISA) in the acute-phase. Other detection methods includes the seroconversion of individuals between acute and convalescent phases and the isolation of virus from the brain following fatal encephalitis [3, 6, 7].

1.2 Rationale for the Development of the WEVEE Vaccine

Alphaviruses have been responsible for multiple epidemics in various parts of the world. There is no effective antiviral treatment or licensed vaccine for any of these encephalitic arboviruses

and treatment is with supportive measures only. Additionally, prevention of viral infection is of particular interest because of the potential use of these viruses as biological weapons.

VLPs are multiprotein structures that mimic the organization and conformation of authentic native viruses without the viral genome. Due to the absence of the viral genome, the VLPs cannot replicate. VLPs contain viral surface proteins that present repetitive linear and conformational epitopes capable of eliciting strong T and B cell immune responses and therefore, are useful as vaccines.

VRC previously developed VRC-CHKVLP059-00-VP, a Chikungunya virus (CHIKV) VLP vaccine. This vaccine demonstrated induction of neutralizing antibodies and protection against CHIKV infection by percutaneous exposure in a rhesus macaque model [8]. Under IND 14907, a Phase 1 clinical trial demonstrated that the vaccine was safe and highly immunogenic in healthy adults [9] and a Phase 2 clinical trial in CHIKV-endemic regions is pending final analysis.

VRC-WEVVLP073-00-VP (or WEVEE) is a trivalent WEE, EEE, and VEE VLP vaccine produced by the same methods as the CHIKV VLP vaccine and is intended to elicit broad spectrum protection against targeted alphaviruses.

1.3 Rationale for the Use of Aluminum–Based Adjuvant

Adjuvants improve the immune response to many vaccines [10, 11]. The most common aluminum-based adjuvants includes aluminum hydroxide, aluminum phosphate, alum (potassium aluminum sulfate), or mixed aluminum salts [12, 13]. Several phenomena contribute to the effect of aluminum hydroxide based adjuvants: a ‘repository effect’ which occurs when the antigens aggregate on the adjuvant particle and are deposited to the immune cell for long duration to induce immune responses, a pro-phagocytic effect, and possibly the activation of the pro-inflammatory nucleotide like receptor protein 3 (NLRP3) dependent pathways [13]. Aluminum-based adjuvants often improve humoral and innate responses and may lead to increased antibody titers, rapid induction of responses, reduction in size or frequency of doses, increased breadth of responses to overcome pathogen diversity, induction of long-lasting immune memory responses, and induction of response to overcome poor immune systems in elderly and young children [14-17]. Aluminum is generally well tolerated, and adjuvants have a demonstrated safety profile over more than six decades of use [14, 15].

1.3.1 Animal Experience with WEVEE VLP and Aluminum-based Adjuvants

Preclinical studies were performed to evaluate the immunogenicity of the trivalent WEVEE VLP vaccines alone and with aluminum hydroxide adjuvant in rabbits and mice.

Mice (n=5/dose) received two intramuscular (IM) injections with WEVEE alone or WEVEE plus alum on days 0 and 28. Antibody responses against WEVEE VLP were evaluated by ELISA every 2 weeks up to 16 weeks. Immune responses were induced faster with adjuvanted VLPs than unadjuvanted VLPs, and adjuvant effect was observed after priming immunization. WEVEE at 15 mcg + alum generated higher antibody responses than other doses of WEVEE with alum. Description of the rabbit and non-human primate (NHP) studies can be found in the Investigator’s Brochure (IB).

1.4 Previous Human Experience

There is no human experience with VRC-WEVVLP073-00-VP. Previous human experience with similar products and with aluminum hydroxide adjuvants are described below.

1.4.1 VRC-CHKVLP-59-00-VP (CHIK VLP) Vaccine and Other VLP Vaccines

VRC-CHKVLP059-00-VP: The CHIKV VLP vaccine was assessed in a Phase 1 open-label, dose-escalation study (VRC 311, NCT01489358) [9]. All injections were well tolerated with no reported arthralgia or fever after vaccination and no reported serious adverse events (SAEs). Solicited reactogenicity parameters were either none or mild; 36% of vaccinees reported mild local reactogenicity and 40% reported mild systemic reactogenicity at least once following vaccination [9]. Neutralizing antibodies were detected in all subjects by 4 weeks after the second dose. A significant boost occurred after the third vaccination in all dose groups. Neutralization titers of vaccine recipients reached levels comparable to those reported after natural infection, suggesting a potentially durable protective response to the vaccine [9]. Antibodies were detected by ELISA in 80-100% of subjects in all three dose groups and geometric mean titers (GMT) were not significantly different between the groups except at week 24. Study results found no significant difference in group GMT 4 weeks after the second dose compared to 4 weeks after the third dose.

This alphavirus CHIKV VLP vaccine was advanced to Phase 2 clinical evaluation in November 2015 in protocol VRC 704 (NCT02562482). Between November 18, 2015 to October 20, 2016, 400 subjects were randomly enrolled into two groups: CHIKV VLP vaccine (n = 201) or PBS placebo (n = 199). Of the 201 participants in the CHIKV VLP vaccine group, 192 received both vaccinations, and 180 completed the study to week 72. Of the 199 participants in the PBS placebo group, 192 received both placebo vaccinations, and 193 completed the study to week 72.

The CHIKV VLP vaccine was well tolerated, with no SAE related to vaccine reported. For local reactogenicity, including pain/tenderness, swelling or redness, 64 (32%) vaccine recipients reported any local symptom, rated as mild or moderate in severity. For systemic reactogenicity, including malaise, myalgia, headache, chills, nausea, joint pain and temperature, 87 (44%) vaccine recipients reported any systemic symptom, rated as mild or moderate in severity. One vaccine recipient (0.5%) experienced a headache graded as severe after the second vaccination. In comparison to placebo, the only significant difference in local reactogenicity was pain/tenderness at the injection site (p-value = 0.005) and there were no significant differences observed in other solicited systemic reactogenicity parameters in vaccine recipients.

Overall, 16 mild-to-moderate AEs evaluated as potentially related to the study product occurred in 11 subjects (neutropenia, bradycardia, hypotension, viral infection, rash, chest pain, dry lips, light headedness, fever, myalgia, gastroenteritis, abdominal pain, anemia, alanine aminotransferase increase, and two hematomas). Of these, AEs (75%) occurred in 8 subjects in the vaccine group, and four AEs (25%) occurred in three subjects in the placebo group. All potentially related adverse events resolved without clinical sequelae.

Other VLP Vaccines: VLPs are considered highly immunogenic and are known to elicit highly neutralizing antibody titers. The FDA has approved several prophylactic VLP vaccines including hepatitis B vaccines (Engerix[®] and Recombivax HB[®], GlaxoSmithKline and Merck, respectively) and human papilloma virus (HPV) vaccines (Cervarix[®] and Gardasil[®],

GlaxoSmithKline and Merck, respectively). Several other VLP vaccine candidates, such as vaccines for influenza, Norwalk and parvovirus, are in pre-clinical or Phase I testing [18, 19].

1.4.2 Human Experience with Other Alphavirus Vaccines

While there are inactivated vaccines for EEEV and WEEV, and live-attenuated and inactivated VEEV vaccines for veterinary use, there are no licensed human vaccines. Human investigational alphavirus vaccines have been used for protection of laboratory workers and other at-risk personnel under FDA IND applications [20]. A live-attenuated VEEV vaccine was developed by the U.S. Army and tested in 821 laboratory workers; minor side-effects (malaise, headache, fever, chills, myalgia, sore throat, nausea, arthralgia, anorexia, vomiting, diarrhea, erythema, rash, urticarial, vasovagal response) were noted in 23% of vaccine recipients and no long term sequelae were reported. At the end of the study, the prime-boost regimen of the live-attenuated VEEV vaccine prime (TC-83) followed by the inactivated VEEV vaccine boost (C-84) induced long-lasting immune response; however, the investigators concluded that a more immunogenic, less reactogenic, single-dose vaccine is needed [21].

Immunologic interference was revealed in sequential or same-day administration of previous generations of inactivated and live-attenuated alphavirus vaccines in animal models and in humans [22-25]. In a retrospective data analysis study with 766 volunteers immunized through a special immunization program at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), subjects who received inactivated EEEV and WEEV vaccines before the live-attenuated VEEV vaccine had significantly lower rates of antibody response than subjects receiving VEEV vaccine before EEEV and WEEV vaccines (66.7% and 80.6%, respectively, $p=0.026$) [24]. Similar findings were reported for the same-day/different arm administration of inactivated EEEV and WEEV vaccines in a cohort of 1401 volunteers immunized through the same program. The overall primary response rate for EEEV vaccines was 66% and for WEEV vaccine was 42% [25].

1.4.3 Previous Human Experience with Aluminum-based Adjuvants

Aluminum adjuvants have been used in vaccines for many decades and with a demonstrated safety profile [26]. Aluminum is the most common adjuvant used in human vaccines licensed by the FDA [27, 28]. Aluminum-containing vaccines have been associated with erythema, subcutaneous nodules, contact hypersensitivity, granulomatous inflammation [26, 29]. A specific limitation is neurotoxicity in patients with decreased renal function [27].

Aluminum-based adjuvants promote strong humoral immune responses, and therefore, are incorporated in vaccines against diseases where neutralizing antibodies are required for protection such as diphtheria, tetanus and hepatitis B [17]. The licensed HPV VLP vaccines, Gardasil (Merck & Co, Inc.) and Cervarix (GlaxoSmithKline), have aluminum in the formulations at 0.5 mg of aluminum hydroxyphosphate sulphate per dose and 0.5 mg of aluminum hydroxide per dose, respectively [18].

As per 21 CFR part 610.15, the amount of aluminum in biological products cannot exceed 0.85 mg/dose. The amount of aluminum in vaccines currently licensed in the US ranges from 0.125-0.85 mg/dose [28]. Based on the FDA regulations, experience with HPV VLP vaccines and VRC pre-clinical data, VRC plans to use 0.5 mg/dose of aluminum hydroxide adjuvant in this Phase 1 study.

1.5 Rationale for Study Design

In this Phase I dose-escalation study, each subject will receive an IM injection via needle and syringe at Day 0 and Week 8. Doses of 6, 30, and 60 mcg of VRC-WEVVLP073-00-VP will be evaluated either alone or with aluminum hydroxide adjuvant. The doses and dosing regimens were selected based on the results of preclinical studies in NHPs (WEVEE Investigator's Brochure and [8]), and results of VRC studies with the CHIKV VLP vaccine, VRC-CHKVLP-59-00-VLP, in animals and in humans [8, 9]. Similar dosing in ranges of 10-60 mcg of VLP per injection and a dosing regimen of three IM injections is used for licensed VLP vaccines against hepatitis B and HPV [18, 30].

1.6 Assessment of Immunogenicity

In this protocol, specimens to evaluate immunogenicity will be taken at baseline and at specified time points. The primary immunogenicity timepoint is 4 weeks after the second vaccination. Measurements of WEVEE-specific humoral immune responses will be assessed by neutralization antibody assays. ELISA and other exploratory assays to assess humoral immune responses may be performed with stored samples. Research samples for immunogenicity assays will be processed at the site and sent directly to the contracted testing laboratory, Battelle, in Columbus, OH. Exploratory immunogenicity assays may also be performed by VRC or contract laboratories, or by other research collaborators.

2 STUDY PRODUCTS

The study products are manufactured under current Good Manufacturing Practices (cGMP). Brief description of the study products are provided in the next sections; for detailed descriptions, please refer to the IB.

2.1 VRC-WEVVLP073-00-VP, Study Product

VRC-WEVVLP073-00-VP (WEVEE) is a sterile, aqueous, buffered solution composed of a 1:1:1 ratio (based on mass) of WEE, EEE, and VEE drug substances to meet a target concentration of 90 mcg/mL (final concentration = 78 mcg/mL). Product is filled into single-dose vials. The formulation buffer consists of 0.8 mM Sodium Phosphate Monobasic Monohydrate, 9.3 mM Sodium Phosphate Dibasic Heptahydrate, 50 mM Sodium Chloride, 5% Sucrose, 5% Sorbitol, and 0.05% Poloxamer 188 at pH 7.8.

2.2 VRC-GENMIX083-AL-VP, Adjuvant

VRC-GENMIX083-AL-VP or Aluminum Hydroxide Suspension (alum, adjuvant) is a sterile, pyrogen-free, suspension filled into glass vials at a nominal fill volume of 0.7 mL ± 0.10 mL to allow withdrawal of 0.5 mL. Aluminum concentration is 5 ± 1 mg/mL.

2.3 VRC-PBSPLA043-00-VP, Diluent

VRC-PBSPLA043-00-VP consists of sterile phosphate buffered saline (PBS) at pH 7.2, aseptically filled at 1.2 mL in a 3 mL glass vial for single use.

2.4 Preclinical Studies of VRC-WEVVLP073-00-VP

Details on preclinical studies conducted with VRC-WEVVLP073-00-VP alone or with adjuvant can be found in the IB.

3 STUDY OBJECTIVES

3.1 Primary Objectives

- To evaluate the safety and tolerability of VRC-WEVVLP073-00-VP in healthy adults when administered IM by needle and syringe at a dose of 6 mcg, 30 mcg or 60 mcg without adjuvant.
- To evaluate the safety and tolerability of VRC-WEVVLP073-00-VP in healthy adults when administered IM by needle and syringe at a dose of 6 mcg, 30 mcg or 60 mcg with adjuvant.

3.2 Secondary Objectives

- To evaluate the humoral immunogenicity of VRC-WEVVLP073-00-VP without adjuvant at 4 weeks after the last product administration by virus-specific neutralization assays.
- To evaluate the humoral immunogenicity of VRC-WEVVLP073-00-VP with adjuvant at 4 weeks after the last product administration by virus-specific neutralization assays.

3.3 Exploratory Objectives

- To evaluate the immunogenicity of VRC-WEVVLP073-00-VP without adjuvant at other timepoints throughout the study.
- To evaluate the immunogenicity of VRC-WEVVLP073-00-VP with adjuvant at other timepoints throughout the study.

4 STUDY DESIGN AND CLINICAL PROCEDURES

This is a Phase I, randomized, open-label, dose-escalation study to examine the dose, safety, tolerability, and immune response to the WEVEE vaccine alone or with alum adjuvant at three doses (6 mcg, 30 mcg, and 60 mcg) in healthy adults. Eligible subjects will be randomized to WEVEE alone or WEVEE plus alum administration in each dose group. The product will be administered IM in the deltoid muscle via needle and syringe at Day 0 and Week 8 in each dose group. The hypotheses are that this vaccine will be safe and elicit specific immune responses to WEE, EEE and VEE viruses.

Group assignments and study schema are shown below in [Table 1](#):

Table 1: VRC 313 Vaccination Schema

VRC 313 Vaccination Schema				
Group	Subjects	Dose	Day 0	Week 8
1	5	6 mcg	WEVVEE	WEVVEE
2	5		WEVVEE + alum	WEVVEE + alum
3	5	30 mcg	WEVVEE	WEVVEE
4	5		WEVVEE + alum	WEVVEE + alum
5	5	60 mcg	WEVVEE	WEVVEE
6	5		WEVVEE + alum	WEVVEE + alum
Total*	30	*Up to 10 subjects over target accrual are permitted to be allocated to any group for additional safety or immunogenicity evaluations.		

4.1 Study Population

All inclusion and exclusion criteria must be met for eligibility.

4.1.1 Inclusion Criteria

A subject must meet all of the following criteria:

1. Age 18 to 50 years
2. Available for clinical follow-up through 36 weeks after randomization
3. Able to provide proof of identity to the satisfaction of the study clinician completing the enrollment process
4. Able and willing to complete the informed consent process
5. Willing to donate blood for sample storage to be used for future research
6. In good general health, without clinically significant medical history, and has satisfactorily completed screening
7. Physical examination and laboratory results without clinically significant findings within the 28 days prior to randomization

Laboratory Criteria within 28 days prior to randomization:

8. Hemoglobin within institutional normal range or accompanied by Principal Investigator (PI) or designee approval
9. White blood cell (WBC) differential either within institutional normal range or accompanied by PI or designee approval
10. Total lymphocyte count: ≥ 800 cells/mm³
11. Platelets: 125,000-500,000/mm³
12. Alanine aminotransferase (ALT): ≤ 1.25 x upper limit of normal range
13. Serum creatinine: ≤ 1.1 x upper limit of normal
14. Negative for HIV infection by an FDA-approved method of detection

Criteria applicable to women of childbearing potential

15. Negative beta-human chorionic gonadotropin (β -HCG) pregnancy test (urine or serum) on day of randomization before receiving the study product
16. Agrees to use an effective method of birth control, if sexually active, from at least 21 days prior to randomization through the last study visit.

4.1.2 Exclusion Criteria

A volunteer will be excluded if one or more of the following conditions apply:

Female-Specific Criteria

1. Breast-feeding or planning to become pregnant while participating in the study

Volunteer has received any of the following:

2. More than 10 days of systemic immunosuppressive medications or cytotoxic medications within the 4 weeks prior to randomization or any within the 14 days prior to randomization
3. Blood products within 16 weeks prior to randomization
4. Immunoglobulin within 8 weeks prior to randomization
5. Prior vaccinations with an investigational alphavirus vaccine
6. Investigational research agents within 4 weeks prior to randomization or planning to receive investigational products while on study
7. Live attenuated vaccines within 4 weeks prior to randomization
8. Inactivated vaccines within 2 weeks prior initial study vaccine administration unless approved by the PI
9. Current anti-TB prophylaxis or therapy

Subject has a history of any of the following clinically significant conditions:

10. A history of confirmed or suspected viral encephalitis infection
11. Serious reactions to vaccines that preclude receipt of study vaccinations as determined by the investigator
12. Hereditary angioedema, acquired angioedema, or idiopathic forms of angioedema
13. Asthma that is not well controlled
14. Diabetes mellitus (type I or type II) with the exception of gestational diabetes
15. Thyroid disease that is not well controlled
16. Hypertension that is not well controlled
17. Evidence of autoimmune disease or immunodeficiency
18. Idiopathic urticaria within the last year
19. Malignancy that is active or history of malignancy that is likely to recur during the study

20. Bleeding disorder diagnosed by a doctor (e.g., factor deficiency, coagulopathy, or platelet disorder requiring special precautions) or significant bruising or bleeding difficulties with IM product administration or blood draws
21. Seizure disorder other than: 1) febrile seizures, 2) seizures secondary to alcohol withdrawal more than 3 years ago, or 3) seizures or treatment for a seizure disorder within the last 3 years
22. Asplenia, functional asplenia or any condition resulting in absence or removal of the spleen
23. Psychiatric condition that precludes compliance with the protocol; past or present psychoses; or within 5 years prior to randomization, a history of suicide plan or attempt
24. Any other chronic or clinically significant medical, psychiatric or social condition that, in the judgement of the investigator is a contraindication to protocol participation or impairs a subject's ability to give informed consent.

4.2 Clinical Procedures And Evaluations

Evaluation of this investigational vaccine will include laboratory tests, medical history, physical examination by clinicians and subject self-assessment. The schedule of study visits is shown in the Schedule of Evaluations in Appendix III.

4.2.1 Pre-screening

Subjects will be recruited through Institutional Review Board (IRB) approved advertising. To identify potential study subjects, study staff may discuss the VRC 313 clinical trial with those who express interest. Study staff may use an interview questionnaire to obtain self-reported medical history in order to determine if the subject may be eligible based on protocol inclusion and exclusion criteria. Potential subjects who appear to be eligible may continue to screen for this study. No study-specific interventions may be done during pre-screening.

4.2.2 Screening

Screening for this study will begin completed after the subject signs an informed consent form (ICF). The screening process may occur over one visit or multiple visits in order for the site to fully assess each subject's eligibility to participate in this study. Screening evaluations must all be completed within the 28-day screening window. The ICF may be signed more than 28 days before study randomization and does not need to be re-signed if outside of this window, unless required by the site's IRB or an updated form becomes available.

Assessment of Understanding: The Assessment of Understanding (AoU) is a tool to help study staff confirm the subject's understanding of the consent information. The AoU must be completed at least once before the subject signs the ICF. Incorrect answers on the AoU must be reviewed with the subject.

Study clinicians must review the ICF with each potential subject. Before screening procedures can be performed, informed consent must be obtained, and the form must be signed, dated and timed by the subject as well as signed and dated by the consentor and a witness. Any member of the research/clinical team can be a witness, but a consentor and a witness should not be the same person at the same time.

The template of the ICF is provided in Appendix I. The site must use the template to develop site-specific forms as needed, adding relevant information as required by the site institutional policies.

During Screening:

- **Medical History and Physical Examination:** Study clinicians must obtain a medical history and perform a physical examination including collection of vital signs, height and weight within 28 days before randomization.
- **Injection Site Assessment:** Clinicians should assess potential injection sites in the deltoid muscle. Clinicians should avoid administering an injection in an area that has an injury, local skin problem or significant tattoo that interferes with evaluation of the injection site after product administration.
- **Pregnancy Prevention Counseling and Pregnancy Testing:** Study clinicians must complete pregnancy prevention counseling on female subjects of childbearing potential to evaluate if subjects are able to meet the birth control eligibility criteria. Pregnancy test results must also be confirmed as negative for these subjects during screening.
- **HIV Prevention Counseling:** During screening, HIV counseling must be completed on all subjects being tested for HIV to ensure the subject is aware of how to reduce risk of and avoid HIV infection. Every attempt must be made to provide the HIV test results to the subjects.
- **Blood Sample Collection:**
 - Samples for clinical evaluation of eligibility criteria must be collected no more than 28 days before randomization. Tests may be repeated as needed based on clinical judgment to confirm eligibility or if there is a suspected change in health status.
 - Samples for research must be collected during screening per Schedule of Evaluations (Appendix III). However, research samples obtained more than 28 days before randomization do not need to be repeated. Some samples collected during screening may be used for assay validation and site proficiency testing.
- **Eligibility Review:** Based on results from the physical examination, medical history evaluation, blood tests and any additional health assessments performed during screening, the study clinicians will determine if subjects qualify to be randomized and receive the study product, and confirm this by documenting on the applicable data collection forms and in the database. For subjects who are not eligible, the reason(s) for ineligibility must be recorded.

4.2.3 Enrollment

All subjects who sign the ICF following completion of the informed consent discussion must be enrolled into the screening segment of the database.

4.2.4 Randomization

Visit 02 (Day 0) is defined as the day of study randomization and first product administration.

If a subject presents with fever or other signs of illness during the first product administration visit, do not randomize the subject and do not order or administer study product. Instead, review

the subject's medical history and conduct a targeted physical examination, as needed. If there are no exclusionary findings or significant illness and the subject becomes well, the randomization visit may be rescheduled within the 28-day allowable screening period. If Visit 02 cannot be rescheduled within the 28-day window, re-test and re-evaluate all required screening parameters in order to ensure eligibility prior to rescheduling the subject for randomization.

Before Randomization:

- **Pregnancy Prevention Counseling and Pregnancy Testing:** Pregnancy prevention counseling must be conducted, and pregnancy test results must be confirmed negative for females of childbearing potential.
- **Medical History Review and Targeted Physical Examination:** Review health status and current medications including recent vaccinations, measure vital signs, and re-assess potential injection sites.
- **Eligibility Confirmation:** Eligibility criteria must be reviewed prior to randomization in the study database.

Randomization: Subjects are electronically randomized upon entry in the database to the open dose group to receive vaccine alone or vaccine plus alum, based on a randomization plan prepared in advance by the Protocol Statistician. Randomization and product administration must both occur on the same day at Visit 02 (Day 0).

Baseline Values for Future Health Assessments: Visit 02 evaluations and medical history that were obtained prior to the first product administration will be used as the baseline for all future safety assessments. If a blood test was not performed at Visit 02 or if results were not obtained due to an error, the values that were obtained during screening evaluations may be used as the baseline for all future safety assessments.

4.2.5 Study Schedule

The Schedule of Evaluations in Appendix III provides details on the study schedule and the permitted visit windows. A clinician should discuss the target dates and timing of the study vaccination(s) and sample collections before completing a randomization to help ensure that the subject can comply with the projected schedule.

The schedule of study visits, permitted windows for completing the visits, and evaluations performed at each visit are shown in Appendix III. After randomization, deviations from the visit windows in completing study visits and study product administrations are discouraged and will be recorded as protocol deviations, but are permitted at the discretion of the IND Sponsor.

Important Information about Shifting Study Visits

Study visits are scheduled a specific number of days apart in order to obtain blood samples for safety and research data at critical time points after each product administration. Note that these days are calendar days and not working business days. Therefore, the "Day of Study" is important to consider when scheduling or rescheduling a subject visit. All study visits are scheduled based on the date of the most recent product administration. Below is further explanation on scheduling.

Visit 02 (Day 0) = first product administration visit. Study Visits 02A through 05 must be scheduled based on the date of the first product administration.

Visit 05 = second product administration visit. Study Visits 05A through 09 must be scheduled based on the date of Visit 05. For example, if Visit 05 occurs +/-7 calendar days outside of the visit window, then Visits 03A through 09 must also be moved ahead +/-7 calendar days. If the second product administration does not occur, then schedule all follow-up visits based on the date of the first product administration.

4.2.6 Product Administration

Before Ordering Study Product: Pregnancy prevention counseling must be conducted, and pregnancy test results must be confirmed negative for females of childbearing potential. Subjects must be clinically evaluated with a medical history review and injection site assessment. Blood samples must be collected after randomization but prior to product administration per Appendix III.

Ordering Study Products: The site must follow standard operating procedures to order study product from the Pharmacy.

Product Administration Procedures: It is recommended, but not required, that the first vaccination be administered into the non-dominant arm. It is preferred, but not required, to alternate arms for a subsequent product administration, if applicable. When choosing an arm for the product administration, clinicians should consider whether there is an arm injury, local skin problem or significant tattoo that precludes the administration of the study product or will interfere with evaluating the arm after product administration. All product administrations will be administered IM into upper arm deltoid muscle by needle and syringe.

For groups receiving adjuvant, the adjuvant will be added by the site pharmacist prior to delivery to the clinic for administration.

Prior to each product administration, the syringe MUST be inverted 5 times. “*Inversion*” of a prepared syringe is defined as a gentle, complete 180 degree rotation, do not “*shake*” the syringe.

For the Second Product Administration: If a subject presents with fever or other signs of significant illness on the day of the product administration visit, do not order or administer study product. Unscheduled visits may be used to evaluate the subject’s condition and the administration visit should be rescheduled within the allowable visit window.

If a subject is undergoing evaluation and/or treatment for a medical condition at the time of the second scheduled administration visit, then vaccinations should be delayed until the condition has resolved or is considered stable. Contact the IND Sponsor for questions about resuming or discontinuing vaccinations as needed.

To schedule a product administration visit outside of the allowable visit window, the site must document PI approval.

Post Product Administration Procedures: Following product administration, all subjects will be observed for a minimum of 30 minutes. Vital signs (temperature, blood pressure, pulse, and respiratory rate) will be collected at least 30 minutes after product administration, prior to subject departure from the clinic. The injection site will be inspected for evidence of local reaction.

In keeping with good medical practice, acute medical care will be provided to subjects for any immediate allergic reactions or other injury resulting from participation in this research study.

4.2.7 Safety Evaluations and Follow-up after Product Administration

Prior to the end of the visit after each product administration, subjects will be given a “Diary Card” to use as a memory aid, on which to record temperature and symptoms daily for 7 days. Subjects will also record the day’s highest measured temperature and measurement of the largest diameter of redness and swelling at injection site.

Subjects will be trained and encouraged to use a secure electronic database but have the option to complete a paper diary card. When the parameters are recorded directly by the subject electronically, the subject’s electronic record will be the source for these data. The paper diary card may be used as a source document. When neither a paper nor electronic diary card is available, the study clinician will note the source of reactogenicity information recorded in the study database.

The solicited signs and symptoms on the diary card will include the following parameters: pain/tenderness at injection site, erythema (redness) at injection site, induration (swelling) at injection site, temperature, unusually tired/feeling unwell, muscles aches (other than at injection site), arthralgia (joint pain), headache, chills and nausea.

Follow-up on subject well-being will be performed by telephone 2 days post each product administration. Subject diaries are reviewed for accuracy and completeness at follow-up in-person visits. Clinicians will follow and collect resolution information for any reactogenicity symptoms that are not resolved within 7 days.

Events following any study product administration that may require clinical evaluation include rash, urticaria, arthralgia, fever of 38.5°C (Grade 2) or higher lasting greater than 24 hours, or significant impairment in the activities of daily living. Additionally, other clinical concerns may prompt a study visit based on the judgment of a study clinician. If a skin lesion or other unexpected reaction at the injection site occurs in this study, we may ask the subject to allow us to take a photograph. If the subject agrees, he/she will be asked to sign a site-specific photography informed consent form.

Any subject who receives at least one vaccination is expected to continue with safety follow-up through study Week 36.

4.2.8 Blood Sample Collection

At intervals throughout the study, blood will be drawn for safety evaluations and immunologic assays. Blood will be drawn from the arm veins of subjects by standard phlebotomy procedures. As per NIH Clinical Center (CC) guidelines, total blood volume drawn from adult subjects (who weigh at least 50 kg) will not exceed 550 mL in any 8-week period. The site must also follow institutional policy for blood collection.

4.2.9 Concomitant Medications

Only routine prescription medications at the time of randomization are recorded in the study database. Subsequently, concomitant medications are only updated or recorded in the database if there is an occurrence of an AE that requires expedited reporting or if the subject develops a new

chronic condition that requires ongoing medical management. Receipt of a FDA-approved vaccine at any time during the study will be recorded in the database (clinicians should work with subjects regarding the timing of licensed vaccines relative to product administration). Otherwise, the concomitant medication changes throughout the study will be recorded in the subject's chart as needed for general medical records, but will not be recorded in the database.

4.3 Dose Escalation

There will be two dose escalation reviews in this study. The Protocol Safety Review Team (PSRT, Section 8.8.1) will conduct an interim safety review of all available data at the time of the review. The PSRT must assess the data as showing no significant safety concerns before escalation to the next dose.

Randomization will begin in Group 1 (6 mcg WEVEE) and Group 2 (6 mcg WEVEE + alum). No more than one subject will be randomized and vaccinated per day for the first 3 subjects at each dose.

- 1) The first interim safety review for dose escalation will be conducted when safety data for the first 3 subjects to receive 6 mcg WEVEE become available for the visit two weeks after vaccination (Visit 03 /Day 14). Subject randomizations and vaccinations in Group 1 and Group 2 may continue during the interim safety review; however, randomizations should be completed prior to beginning Group 3 and 4 randomizations.

If the 6 mcg dose of WEVEE is assessed as not showing safety concerns by the PSRT, randomization can begin for Group 3 and Group 4.

Randomization will proceed in Group 3 (30 mcg WEVEE) and Group 4 (30 mcg WEVEE + alum).

- 2) The second interim safety review for dose escalation will be conducted when safety data for the first 3 subjects to receive 30 mcg WEVEE become available for the visit two weeks after vaccination (Visit 03 /Day 14). Subject randomizations and vaccinations in Group 3 and Group 4 may continue during the interim safety review; however, randomizations should be completed prior to beginning Group 5 and 6 randomizations.

If the 30 mcg dose is assessed as safe, randomization can begin for Group 5 (60 mcg WEVEE) and Group 6 (60 mcg WEVEE + alum).

If an initial study vaccination is not completed or there are discontinuations from the study before there are sufficient data to conduct the dose escalation review, then extra subjects may be randomized at the same dose level in order to have the requisite data on at least 3 subjects in these groups. The IRB will be provided with documentation of the safety review process and notification of the dose escalation. Consultation with the IRB and FDA, if needed, as per study pause criteria ([Section 4.4](#)) will occur if indicated by the review. One outcome of a dose escalation review may be to recommend evaluation of additional subjects at the current dose level and reassess for safety before proceeding to a higher dose level.

4.4 Pausing and Resuming the Study

4.4.1 Criteria for Pausing the Study

The Protocol Chairs, in consultation with site PI, will closely monitor and analyze study data as they become available and will make determinations regarding the presence and severity of AEs. The administration of study products and new enrollments will be paused and the IND Sponsor will be promptly notified according to the following criteria:

- **One** (or more) subject experiences a **SAE** assessed as related to the study product (with or without adjuvant).
- **Two** (or more) subjects experience the same **Grade 3 or higher AE** assessed as related to the study product (with or without adjuvant). Pause is not required for self-limited solicited reactogenicity (generally defined as resolved within 2 days of onset) following any study vaccination.
- **Three** (or more) subjects experience the same or similar **Grade 3 solicited AE** (other than injection site redness or swelling) lasting ≥ 24 hours.

4.4.2 Plan for Review of Pauses and Resuming the Study

Study randomizations and product administrations would resume only if review of the events that caused the pause resulted in a recommendation to permit further randomizations and product administrations. The review to make this decision will occur as follows:

- The IND Sponsor, with participation by the Protocol Chairs and site PI, will conduct the review and make the decision to resume or close the study for any SAEs or AEs that meet the criteria for pausing the study.
 - As part of the pause review, the reviewers will also advise on whether the study needs to be paused again for any subsequent AEs of the same type. The FDA and the IRB will be notified of SAE and Grade 3 or higher pause reviews and of the IND Sponsor's decisions.

4.4.3 Dose-Limiting Toxicity

Dose-limiting toxicity is defined in this protocol as an AE that prevents a dose escalation of the study vaccine or prevents continuation of product administrations at a given dose level. If the study is paused as per criteria in [Section 4.4.1](#) and a decision is made to not resume the study vaccinations at the current dose, then the safety review will include a decision as to whether or not to continue accrual at a lower vaccine dose that was evaluated to be safe in order to achieve the target study accrual of 30 subjects.

4.5 Discontinuation of Product Administrations or Study Participation

Decisions to discontinue giving the second product administration or to discontinue protocol participation for a subject will be made by the site PI or designee.

4.5.1 Discontinuation of Product Administrations

A subject may be discontinued from receiving study product for the following reasons:

1. Pregnancy;
2. Grade 3 adverse event assessed as related to the study product (with the exception that self-limited Grade 3 solicited reactogenicity does not require discontinuation of study injections);
3. Grade 4 adverse event assessed as related to the study product;
4. Immediate hypersensitivity reaction associated with the study product;
5. Intercurrent illness that is not expected to resolve prior to the next scheduled study product administration;
6. Treatment with systemic glucocorticoids (e.g., prednisone or other glucocorticoid) or other immunomodulators (other than nonsteroidal anti-inflammatory drugs [NSAIDs]), with the exception that study product administration may continue per site PI discretion if the next one occurs at least 2 weeks following completion of glucocorticoid treatment;
7. The IND Sponsor and/or PI assess that it is not in the best interest of the subject to continue receiving study product.

Subjects who receive at least one study product will continue follow-up according to the Schedule of Evaluations, except that the research sample collections will be discontinued for pregnant women or others in which it is contraindicated.

4.5.2 Discontinuation from Protocol Participation

A subject may be discontinued from protocol participation for the following reasons:

1. Subject voluntarily withdraws
2. Subject develops a medical condition that is a contraindication to continuing study participation
3. The IND Sponsor or regulatory authorities stop the protocol
4. The IND Sponsor and/or PI assess that it is not in the best interest of the subject to continue participation or that the subject's compliance with the study is not sufficient
5. Co-enrollment into a study in which other investigational research agents will be administered before the subject has completed the follow-up after the last WEVEE vaccine administration;

5 SAFETY AND ADVERSE EVENTS

5.1 Adverse Events

An adverse event (AE) is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the study product.

Each AE will be graded according to the Table for Grading Severity of Adverse Events (see [Appendix IV](#)). The following guidelines will be used to determine when or not an AE should be recorded in the study database:

- From the time that subject signs the ICF, only AE that meet the definition of a SAE as described in Section 5.2 that occur within 24 hours of a screening visit will be reported.
- Solicited AEs (i.e, reactogenicity parameters) will be recorded in the study database per diary card entries for 7 days after each product administration and is not recorded with attribution assessments. Clinicians will follow and collect resolution information for any reactogenicity symptoms that are not resolved within 7 days.
- Unsolicited AEs and attribution assessments will be recorded in the study database from receipt of the first product administration through the visit scheduled for 4 weeks after each product administration. At other time periods between product administrations and when greater than 4 weeks after the last study product administration, only SAEs (as detailed in [Section 5.2](#)) and new chronic medical conditions that require ongoing medical management are recorded through the last study visit.

5.2 Serious Adverse Events

The term “serious adverse event” (SAE) as defined in US 21 Code of Federal Regulations (CFR) 312.32 as follows: “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, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or 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.”

“Life threatening” refers to an AE that at occurrence, represented an immediate risk of death to the subject. An event that hypothetically may cause death if it occurs in a more severe form is not considered life-threatening. Similarly, a hospital admission for an elective procedure is not considered a SAE.

5.3 Adverse Event Reporting to the IND Sponsor

All AEs that meet the definition of a SAE must be reported from receipt of the first product administration through the last study visit by the study site and submitted on an expedited basis to the IND Sponsor, VRC, according to sponsor guidelines as follows:

- results in death
- is life threatening
- results in persistent or significant disability/incapacity

- requires unplanned inpatient hospitalization or prolongation of existing hospitalization
- is a congenital anomaly/birth defect in the offspring of a study subject
- is an important medical event that may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above.

In addition, any event, regardless of severity, which in the judgment of an investigator represents a SAE, may be reported on an expedited basis.

The site investigator will communicate an initial SAE report within 1 business day of site awareness of occurrence to the IND Sponsor by data entry in the database. Any SAE entered into the study database will generate an automatic email notification to the IND Sponsor. The site must remove personal identifying information about the subject from SAE case reports before submission to the IND Sponsor.

A full written report by the site investigator should be submitted to the IND Sponsor within 3 working days and as soon as possible in case of death. In order for the IND Sponsor to comply with regulations mandating sponsor notification of specified SAEs to the FDA within 7 or 15 calendar days, the investigator must submit additional information as soon as it is available.

5.3.1 IND Sponsor Reporting to the FDA

It is the responsibility of the IND Sponsor to make the determination of which SAEs are “serious and unexpected suspected adverse reactions” (SUSARs) as defined in 21 CFR 312.32.

- *Suspected adverse reaction* means any AE for which there is a reasonable possibility that the drug caused the AE.
- *Unexpected adverse event* means an AE that is not listed in the IB or is not listed at the specificity or severity that has been observed.

All SUSARs, as determined by the IND Sponsor, will be reported to the FDA as IND Safety Reports. All IND Safety Reports will be provided to the site PI by the IND Sponsor or delegated representative.

The IND Sponsor will submit an IND Annual Report of the progress of the investigation to the FDA as defined in 21 CFR 312.33.

5.4 Reporting to the Institutional Review Board

The site should follow the reporting procedures and requirements established by the site IRB. The definitions below are provided as guidance and should not supersede the site’s IRB policies. The FDA “Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting to IRBs – Improving Human Subject Protection” is recommended for use and can be found at the following location:

<https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126572.pdf>.

5.4.1 Unanticipated Problems

An unanticipated problem (UP) is defined as any incident, experience, or outcome that meets all three of the following criteria:

- unexpected in nature, severity, or frequency in relation to the research risks that are described in the protocol, informed consent, IB, other study documents or in consideration of the characteristics of the subject population being studied; **and**
- related to participation in the research; **and**
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Serious UP: An UP that meets the definition of a SAE or compromises the safety, welfare or rights of subjects or others.

An UP that is not an AE (UPnonAE) is an unanticipated problem that does not fit the definition of an AE, but which may, in the opinion of the investigator, involve risk to the subject, affect others in the research study, or significantly impact the integrity of research data. Such events may also be considered a UP. For example, we will report occurrences of breaches of confidentiality, accidental destruction of study records, or unaccounted-for study drug.

5.4.2 Protocol Deviations

A protocol deviation is defined as any change, divergence, or departure from the IRB-approved study procedures in a research protocol. Protocol deviations are designated as serious or non-serious and further characterized as:

- Those that occur because a member of the research team deviates from the protocol.
- Those that are identified before they occur, but cannot be prevented.
- Those that are discovered after they occur.

Serious Protocol Deviation: A deviation that meets the definition of a SAE or compromises the safety, integrity of the data, welfare or rights of subjects or others.

5.4.3 Non-Compliance

Non-compliance is the failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human subjects. Non-compliance is further characterized as serious, continuing or minor.

“Serious non-compliance” is defined as non-compliance that

- Increases risks, or causes harm, to participants
- Decreases potential benefits to participants
- Compromises the integrity of the NIH-HRPP
- Invalidates the study data

“Continuing non-compliance” is non-compliance that is recurring.

“Minor non-compliance” is non-compliance that is neither serious nor continuing.

5.4.4 Expedited and Annual Reporting to the site IRB

Expedited and annual reporting to the site IRB will be completed by the site per the institutional requirements.

6 STATISTICAL CONSIDERATIONS

6.1 Overview

This study is a Phase I, randomized, open-label, dose-escalation study to examine the dose, safety, tolerability, and immunogenicity of VRC-WEVLP073-00-VP (WEVEE) alone or with alum adjuvant at Day 0 and Week 8. The primary objective relates to safety and tolerability; the secondary and exploratory objectives relate to the immunogenicity of the study product.

6.2 Endpoints

6.2.1 Primary Endpoints: Safety

Assessment of product safety will include clinical observation and monitoring of hematological and chemical parameters. Reactogenicity will be closely monitored for 7 days after each product administration and safety evaluated by clinical visits through the study duration of 36 weeks.

The following parameters will be assessed for all study groups:

- Local reactogenicity signs and symptoms for 7 days after each injection
- Systemic reactogenicity signs and symptoms for 7 days after each injection
- Laboratory measures of safety
- AEs
- SAEs
- New chronic medical conditions

6.2.2 Secondary Endpoints: Immunogenicity

The immunogenicity endpoints are antigen-specific antibody responses as evaluated by virus-specific neutralization assays. The primary time point for immunogenicity evaluation is 4 weeks after the second vaccination.

6.2.3 Exploratory Endpoints: Immunogenicity

Exploratory immunogenicity endpoints are measured by virus-specific neutralization assays, ELISA, and other research tests as described in Section 1.6

6.3 Sample Size and Accrual

Recruitment will target 30 healthy adult participants divided equally among 6 groups.

6.3.1 Power Calculations for Safety

The goal of the safety evaluation for this study is to identify safety concerns associated with product administration of the investigational vaccine. Primary sample size calculations for safety are expressed in terms of the ability to detect serious adverse experiences.

The ability of the study to identify SAEs will be expressed in terms of the probability of observing a certain number of SAEs. Useful values are the minimum true rate such that the probability of observing at least one event is at least 90%, and the maximum true rate such that the probability of not observing any event is at least 90%. Within each group (n=5), there is over 90% chance to observe at least 1 SAE if the true rate is at least 0.37 and over 90% chance to observe no SAE if the true rate is no more than 0.02.

Probabilities of observing 0 or more than 1 SAE within each group are presented in Table 2 for a range of possible true event rates. These calculations provide a more complete picture of the sensitivity of this study design to identify potential safety problems with the vaccine.

Table 3 gives the upper and lower bounds for 95% exact binomial confidence intervals of the true SAE rate at all possible numbers of events within each group (n=5). If none of the 5 vaccines experience serious adverse events, the 95% exact 2-sided upper confidence bound for the SAE rate is 0.522.

Table 2: Probability of Events for Different Safety and Immunogenicity Scenarios within a Group (n=5)

True Event rate	Pr (observing 0 event)	Pr (observing more than 1 event)
0.005	0.975	0
0.01	0.951	0.001
0.02	0.904	0.004
0.035	0.837	0.011
0.05	0.774	0.023
0.1	0.59	0.081
0.15	0.444	0.165
0.2	0.328	0.263
0.3	0.168	0.472

Table 3: 95% Confidence Intervals for the True Rate At All Possible Observed Rates within a Group (n=5)

Observed Rate	95% Confidence Interval	
	Lower Bound	Upper Bound
0/5	0	0.522
1/5	0.005	0.716
2/5	0.053	0.853
3/5	0.147	0.947
4/5	0.284	0.995
5/5	0.478	1

6.3.2 Sample Size Calculations for Immunogenicity

Table 2 gives the probabilities of observing 0 or at least 2 responses over a range of underlying response rates. For example, if the true response rate at a particular time point is 0.20, then there is a probability of 0.672 to observe at least one response and a probability of 0.263 to observe at least 2 responses among the 5 vaccinees in a group.

Table 3 is applicable to the immunogenic response rates, and gives the exact 95% confidence interval of the true response rate over possible number of responses out of the 5 subjects. For example, if we observe 2 responses among the 5 vaccinees, the 95% exact binomial confidence interval of the true response rate will range from 0.053 to 0.853.

6.3.3 Power for Comparison

For groupwise difference in immunogenicity, a simple comparison on the positive response rate will be used. Table 4 gives the power of Fisher exact test to compare any two schedules over a range of possible response rates and indicates that this study is not powered for group comparison.

Table 4: Power (%) to Detect Difference in Response Rates between Two groups by Fisher’s Exact Test, Each Group of Size n=5

		Arm 1 Rate (n=5)			
		0.2	0.3	0.4	0.5
Arm 2 Rate (n=5)	0.1	1	1	5	12
	0.2	1	1	3	7
	0.5	7	4	2	2
	0.6	14	8	4	2

6.4 Statistical Analysis

Since randomization is concurrent with receiving the first study vaccination, the expectation is that all randomized participants will receive at least one vaccination and therefore will provide some safety data. All statistical analyses will be performed using Statistical Analysis System (SAS) or statistical software R. No formal multiple comparison adjustments will be employed for safety endpoints or immunogenicity endpoints.

6.4.1 Analysis Variables

The analysis variables consist of baseline variables, safety variables, and immunogenicity variables for primary and secondary objective analyses.

6.4.2 Baseline Comparability

Baseline characteristics including demographics and laboratory measurements will be summarized using descriptive statistics.

6.4.3 Safety Analysis

Reactogenicities

The number and percentage of participants experiencing each type of reactogenicity sign or symptom will be tabulated by severity. For a given sign or symptom, each participant's reactogenicity will be counted once under the maximum severity for all assessments.

Adverse Experiences

Adverse experiences are coded into Medical Dictionary for Regulatory Activities (MedDRA) preferred terms. The number and percentages of participants experiencing each specific adverse event will be tabulated by severity and relationship to treatment. For the calculations in these tables, each participant's adverse experience will be counted once under the maximum severity or strongest recorded causal relationship to treatment.

A complete listing of adverse experiences for each participant will provide details including severity, relationship to treatment, onset, duration and outcome.

Local laboratory values

Boxplots of local laboratory values will be generated for baseline values and for values measured during the course of the study. Each boxplot will show the 1st quartile, the median, and the 3rd quartile. Outliers, or values outside the boxplot, will also be plotted. If appropriate, horizontal lines representing boundaries for abnormal values will be plotted.

6.4.4 Immunogenicity Analysis

The statistical analysis for immunogenicity will employ the intent-to-treat principle, i.e., all data from randomized participants will be used. In the final analysis of immunogenicity, if there are cases of a subject receiving a schedule different from the assignment, then an as-treated analysis will be performed.

If assay data are qualitative (i.e., positive or negative) then analyses will be performed by tabulating the frequency of positive response for each assay at each time point that an assessment is performed. Binomial response rates will be presented with their corresponding exact 95% confidence interval estimates. Fisher's exact tests will be used to compare the two vaccine groups to each other. Missing responses will be assumed to be missing at random, i.e., conditional on the observed data the missingness is independent of the unobserved responses. Graphical descriptions of the longitudinal immune responses will also be given.

Some immunologic assays have underlying continuous or count-type readout that is often dichotomized into responder/nonresponder categories. For these assays, graphical and tabular summaries of the underlying distributions will be made. These summaries may be performed on transformed data (e.g., log transformation) to better satisfy assumptions of symmetry and homoscedasticity.

6.4.5 Missing Data

Missing responses will be assumed to be missing completely at random. Analyses will include all samples available at each study time point.

6.4.6 Interim Analyses of Immunogenicity

An interim analysis of immunogenicity data may be performed when half of vaccinated participants reach the primary endpoint for immunogenicity evaluation at 4 weeks after the last product administration. Reports will be provided to the Protocol Chairs, and other key VRC investigators solely for the purpose of informing future trial-related decisions in a timely manner. Results will remain confidential and should in no way influence the conduct of the VRC 313 trial in terms of early termination or later safety or immunogenicity endpoint assessments.

6.5 Randomization of Intervention Assignments

Randomizations will be done online using an electronic randomization system. The randomization code will be prepared by the Protocol Statistician and included in the randomization module for the trial. The randomization code will link to the intervention assignment. The electronic data system will assign each subject a randomization code after eligibility has been confirmed in the system.

At the beginning of the study, subjects will be randomized 1:1 to Groups 1 and 2. If the criteria for the first dose escalation are met and procedures for the interim safety review are completed, subjects can be randomized 1:1 to Groups 3 and 4. For practical purposes, accrual and randomization to Groups 1 and 2 should be completed as per study plan before accrual to Groups 3 and 4 begins.

If the criteria for the second dose escalation are met and procedures for the interim safety review are completed, subjects can be randomized 1:1 to Groups 5 and 6. For practical purposes, accrual and randomization to Groups 3 and 4 will be completed as per study plan before accrual to Groups 5 and 6 begins.

The subject and study clinicians will be informed on the subject's group assignment upon completing randomization in the electronic data collection system.

To decrease the potential for subject dropouts during the period between randomization and product administration will occur on Day 0 when eligibility is confirmed. If subjects accrued to a study group do not complete the number of vaccinations and follow-up duration specified, then additional subjects may be accrued in that group.

7 PHARMACY PREPARATION AND ADMINISTRATION PROCEDURES

The study groups and study vaccine dosing schedule are shown in the Vaccination Schema in Section 4. Refer to the IB for further information about the investigational study products.

7.1 Study Products

This clinical trial includes one investigational vaccine, one adjuvant, and one diluent as follows:

- VRC-WEVVLP073-00-VP, 78 mcg/mL in formulation buffer filled to a volume of 1.2 mL in a 3 mL single dose vial.
- Aluminum Hydroxide Suspension (alum) as adjuvant at a concentration of approximately 5 mg/mL at a volume of 0.7 mL in a 3 mL single dose vial.

- VRC-PBSPLA043-00-VP, phosphate buffered saline (PBS), pH 7.2, as diluent filled to a volume of 1.2 mL in a 3 mL single dose vial.

All study products were manufactured under cGMP by the VRC Pilot Plant and must meet lot release specifications prior to administration for use in the clinical study. All subjects in this trial are scheduled to be vaccinated with a single lot of vaccine.

When released for use in the clinical trial, the vials are shipped to the study pharmacist using appropriate shipping arrangements according to Leidos Biomedical VCMP SOPs.

7.2 Study Product Presentation, Stability, and Storage

7.2.1 Labels

At the time of study product delivery to the pharmacy, labels on study products, VRC-WEVLP073-00-VP and VRC-PBSPLA043-00-VP, will have specific product information (e.g., product description, VRC product number, lot number, fill volume, concentration, fill date, storage condition). Labels will contain an Investigational Use Statement (“Limited by Federal Law to Investigational Use”), and manufacturer information.

7.2.2 Stability

All study agents and diluent are placed on stability testing at the VRC Pilot Plant. Stability studies are performed according to International Conference of Harmonisation (ICH) guidelines. Vials are intended for single use only and thus do not contain a preservative.

7.2.3 Storage

Study products will be shipped to the study pharmacy at the recommended temperature range using appropriate shipping arrangements according to Leidos Biomedical VCMP SOPs.

VRC-WEVLP073-00-VP: Vials of vaccine are stored until use at $\leq -60^{\circ}\text{C}$ in a qualified, continuously monitored temperature-controlled freezer (DO NOT STORE AT -45°C to -10°C). Vials, intended for single use only and should not be refrozen after thaw. Vaccine vials are removed from the freezer and equilibrated to room temperature prior to product administration.

VRC-GENMIX083-AL-VP: Vials of alum are stored until use at 2°C to 8°C in a qualified, continuously temperature monitored refrigerator. Do not freeze. Vials of adjuvant are intended for single use only.

VRC-PBSPLA043-00-VP: Vials of PBS are stored until use between -45°C to -10°C in a qualified, continuously temperature monitored, non-frost-free freezer. Vials of diluent are intended for single use only and should not be refrozen after thawing.

7.2.4 Deviations in Temperatures

Temperature excursions that are outside of the specified ranges will be reported per pharmacy guidelines. If deviations in storage temperature occur from the the normal allowance as described in the IB, the site pharmacist or designee must report the storage temperature excursion promptly to the PI and IND Sponsor and product must be quarantined in a separate area.

The excursion must be evaluated and investigated and action must be taken to restore and maintain the desired temperature limits. Pending the outcome of the investigation, the IND Sponsor will notify the pharmacist or designee if continued clinical use of the product is acceptable.

7.3 Preparation of Study Product for Administration

Refer to the IB for information on study products preparation and use. Refer to the group assignment for the study subject to select the proper product type.

The pharmacy will label the syringe before delivery to the clinic with the subject identifier, the date, and the time allowance for administration. The injection must be administered within 2 hours after removing the vial from the freezer.

VRC-WEVVLP073-00-VP is supplied in a 3 mL glass vial with 1.25 mL of vaccine at a concentration of 78 mcg/mL. Vials contain a clear solution; some small white translucent particles may be visible. Vials with visible particles may be used. Vials are intended for single use only and thus do not contain a preservative.

The following general instructions apply to preparing all vaccine doses (alone and with adjuvant) for product administration:

1. Preparation will be done by a Pharmacist in a clean preparation unit with limited access.
2. Prepare all doses under sterile conditions.
3. Thaw the vial(s) containing VRC-WEVVLP073-00-VP at room temperature (15-27°C); acclimate vials of adjuvant to the same temperature.
4. Keep the material at room temperature or refrigerated during the entire preparation period until product administration (no longer than 2 hours following removal of vial from the freezer).
5. Keep the prepared study product out of direct sunlight.
6. All preparation instructions assume the exact dose withdrawn will be administered; draw more if an overage is needed for study product accuracy.
7. “*Inversion*” of a prepared vial or syringe is defined as a gentle, complete 180 degree rotation of the container. Therefore, when instructed to “*invert*”, do not “*shake*” the product or syringe.

7.3.1 Preparation of VRC-WEVVLP073-00-VP

Preparation of Vaccine Alone (6 mcg dose)

1. Transfer 2.4 mL PBS diluent to a new container (sterile polypropylene microcentrifuge tube or glass vial).
2. Add 0.2 mL WEVEE vaccine to the same container.
3. Invert 5x to mix.
4. Withdraw 1.0 mL into a syringe.
5. Invert 5X to mix immediately prior to administration.

Preparation of Vaccine Alone (30 mcg dose)

1. Transfer 0.8 mL PBS diluent to a new container (sterile polypropylene microcentrifuge tube or glass vial).
2. Add 0.5 mL WEVEE vaccine to the same container.
3. Invert 5x to mix.
4. Withdraw 1.0 mL into a syringe.
5. Invert 5X to mix immediately prior to administration.

Preparation of Vaccine Alone (60 mcg dose)

1. Transfer 0.3 mL PBS diluent to a new container (sterile polypropylene microcentrifuge tube or glass vial).
2. Add 1.0 mL WEVEE vaccine to the same container.
3. Invert 5x to mix.
4. Withdraw 1.0 mL into a syringe.
5. Invert 5X to mix immediately prior to administration.

7.3.2 Preparation of VRC-WEVLP073-00-VP plus Adjuvant

Preparation of Vaccine with Adjuvant (6 mcg + alum)

1. Gently invert vial of aluminum hydroxide 5x to create a suspension. Transfer 0.26 mL aluminum hydroxide suspension to a new container (sterile polypropylene microcentrifuge tube or glass vial).
2. Add 2.1 mL PBS Diluent.
3. Add 0.2 mL WEVEE Vaccine.
4. Invert 5x to mix and hold at ambient temperature for a minimum of 15 minutes.
5. Withdraw 1.0 mL into a syringe.
6. Invert 5X to mix immediately prior to administration.

Preparation of Vaccine with Adjuvant (30 mcg + alum)

1. Gently invert vial of aluminum hydroxide suspension 5x to create a suspension. Transfer 0.13 mL adjuvant to a new container (sterile polypropylene microcentrifuge tube or glass vial).
2. Add 0.67 mL PBS Diluent.
3. Add 0.5 mL WEVEE Vaccine.
4. Invert 5x to mix and hold at ambient temperature for a minimum of 15 minutes.
5. Withdraw 1.0 mL into a syringe.
6. Invert 5X to mix immediately prior to administration.

Preparation of Vaccine with Adjuvant (60 mcg + alum)

1. Gently invert vial of aluminum hydroxide suspension 5x to create a suspension. Transfer 0.13 mL adjuvant to a new container (sterile polypropylene microcentrifuge tube or glass vial).
2. Add 0.17 mL PBS Diluent.
3. Add 1.0 mL WEVEE Vaccine.
4. Invert 5x to mix and hold at ambient temperature for a minimum of 15 minutes.
5. Withdraw 1.0 mL into a syringe.
6. Invert 5X to mix immediately prior to administration.

7.4 Study Product Administration

The vaccine will be prepared in the pharmacy and the prepared syringe containing vaccine will be delivered to the clinic for administration. The study product must be administered within 2 hours after removing the vial from the freezer. The plan for product administration is to use standard injection technique. Immediately prior to administration invert the syringe end-over-end 5x to mix. The study product will be administered IM into the deltoid muscle by needle and syringe.

7.5 Study Product Accountability

7.5.1 Documentation

The site will be responsible for maintaining an accurate record of the inventory and an accountability record of the investigational study products supplied for this study. Electronic documentation as well as paper copies may be used.

7.5.2 Disposition

The empty vials and the unused portion of a vial will be discarded on the same day of use in a biohazard containment bag that will be incinerated or autoclaved per site policy. Any unopened vials that remain at the end of the study will be discarded at the discretion of the IND Sponsor in accordance with policies that apply to investigational products. Partially used vials or expired prepared doses cannot be administered to other subjects nor used for *in vitro* experimental studies and will be discarded as indicated above.

8 HUMAN SUBJECT PROTECTIONS AND ETHICAL OBLIGATIONS

This research will be conducted in compliance with the protocol, Good Clinical Practices guidance, and all applicable regulatory requirements.

8.1 Institutional Review Board

The protocol, proposed ICF, other written subject information, and any proposed advertising material will be submitted to the site IRB for written approval.

The site PI must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the ICF. The site PI is responsible for ensuring proper IRB notifications of protocol deviations or SAEs occurring at the site and other AE reports received from the VRC, in accordance with the protocol and the site IRB policy.

The site PI will be responsible for obtaining annual IRB approval/renewal throughout the duration of the study. Documentation of the IRB approval must be provided to the IND Sponsor.

8.2 Subject Recruitment and Randomization

All study activities will be carried out at the approved study site. Subjects for this study will be recruited through IRB approved advertising by the site in accordance with the site IRB standards for recruitment practices.

Effort will be made to include women and minorities in proportions similar to that of the community from which they are recruited.

8.2.1 Participation of Children

Children are not eligible to participate in this clinical trial because it is the first study in humans with the investigational vaccine and does not meet the guidelines for inclusion of children in research according to 45 CFR 46, Subpart D, 401-409. If the product is assessed as safe and immunogenic, other protocols designed for children may be conducted in the future.

8.2.2 Participation of Site Employees

The study site will follow institutional policies related to study participation of site employees. Neither participation nor refusal to participate will have an effect, either beneficial or adverse, on the subject's employment or work situation.

8.3 Informed Consent

The template study ICF is provided in [Appendix I](#). It describes the investigational products to be used and all aspects of protocol participation. Before a subject's enrollment in the study, it is the investigator's responsibility to obtain written informed consent from the subject, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific procedures or study medications are administered.

An IRB-approved Assessment of Understanding (AoU) quiz, intended to assist in the evaluation of the subject's understanding of this study, is administered as part of the consent process. The AoU should be completed prior to randomization, and verbalized understanding of all questions answered incorrectly should be confirmed with a subject.

The acquisition of informed consent will be documented in the subject's medical records, as required by 21 CFR 312.62, and the ICF will be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The original signed ICF will be placed in the medical record and a copy of the signed ICF will be provided to the subject.

8.4 Subject Confidentiality

The site investigator must ensure that the subject's anonymity is maintained, and will ensure that no information identifying the subject will be released to any unauthorized party. Personally

identifiable information will not be identified in any reports on this study. All records will be kept confidential to the extent provided by federal, state and local law. Medical records are made available for review when required by the FDA or other authorized users, such as the vaccine manufacturer, only under the guidelines set by the Federal Privacy Act. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform the subjects that the above named representatives will review their study-related records without violating the confidentiality of the subjects. Stored study research samples are labeled by a code (such as a number) that only the study team can link to the subject. The requirement to maintain subject confidentiality is included in the study informed consent document.

8.5 Risks and Benefits

8.5.1 Risks of the WEVEE Vaccine

There is no prior human experience with administration of VRC-WEVVLP073-00-VP in healthy adults. First human clinical trials of a similar VLP vaccine, VRC 311 - CHIKV VLP, determined that doses in the range of 10-40 mcg were safe for further evaluation in healthy adults. The solicited local and systemic signs and symptoms following administration of the CHIKV VLP were generally none to mild. In VRC 311, seven laboratory test AEs (occurring in four participants) were assessed as related to study vaccine based on temporal relationship to vaccination. The AEs included four mild transient alanine aminotransferase increases and two mild and one moderate transient neutropenia. All resolved without clinical sequelae.

This alphavirus CHIKV VLP vaccine was advanced to Phase 2 clinical evaluation in November 2015 in protocol VRC 704. As of November 13, 2017, 400 subjects have received a total of 780 injections of VRC-CHKVLP059-00-VP or placebo. There have been no serious adverse events (SAEs) assessed as related to the study product reported in the study and no AEs that required expedited reporting to the FDA. Abnormalities in blood laboratory parameters observed in the study were asymptomatic, predominantly mild or moderate in severity. The local and systemic reactogenicity signs and symptoms following administration of the CHIKV VLP were generally mild to moderate. All abnormalities in blood laboratory parameters, solicited local and systemic reactogenicity signs and symptoms were resolved without clinical sequelae.

Potential side effects resulting from IM injection include stinging, arm discomfort, redness of the skin or mild bruising at product administration sites.

Subjects may exhibit general signs and symptoms associated with administration of a vaccine, including fever, chills, rash, aches and pains, nausea, headache, dizziness and fatigue. These side effects will be monitored, but are generally short term, mild to moderate severity and usually do not require treatment.

There may be other unknown side effects.

8.5.2 Risks of Aluminum Hydroxide Suspension

Aluminum is the most common adjuvant used in human vaccines licensed by the FDA [27] used in literally billions of individuals over decades of clinical use [14]. Adverse effects are generally limited to minor local reaction at the injection site [14]. Other more severe local reactions like

erythema, subcutaneous nodules, contact hypersensitivity and granulomatous inflammation may occur [28].

8.5.3 Risks of Phosphate Buffered Saline

PBS will be used as a diluent for the vaccine. No AEs are anticipated from the use of this product.

8.5.4 Other Risks

Blood collection procedures are common in routine medical practice. The risks of blood sample collection are minimal and consist of mild discomfort at the blood collection site. The procedure may cause mild pain, bruising, fainting, and, rarely, infection at the blood collection site.

We do not know the possible effects of the study vaccine on the fetus or nursing infant. Therefore, females of childbearing potential will be tested for pregnancy prior to each product administration.

It is possible that the standard medical tests performed as part of this research protocol will result in new diagnoses. Depending on the medical findings and consequences of being provided with the new medical information about health status, the study subject may view this aspect of study participation as either a risk or a benefit. Any such information will be shared and discussed with the subject and, if requested by the subject, will be forwarded to the subject's primary health care provider for further workup and management.

8.5.5 Benefits

Study subjects will not receive direct health benefit from study participation. This protocol is not designed to provide treatment for any condition. Others may benefit from knowledge gained in this study that may aid in the development of the WEVEE vaccine. The investigational vaccine is not expected to provide protection from WEEV, EEEV, and VEEV infection.

8.6 Plan for Use and Storage of Biological Samples

To be eligible for this protocol, subjects must be willing to allow stored specimens to be used in the future for studying infectious diseases, immune function, vaccine responses, and other medical conditions. If tests show evidence of any acute or chronic condition, subjects will be informed of the results and advised to seek appropriate medical care for the condition. In general, testing performed at a research laboratory is not for diagnostic purposes and results will not be available to the study site or study subject.

The plan for use and storage of biological samples from this protocol is as outlined in the following sections.

8.6.1 Use of Samples, Specimens and Data

Samples, specimens and data collected under this protocol may be used to conduct protocol-related safety and immunogenicity evaluations, exploratory laboratory evaluations related to the type of infection the vaccine was designed to prevent, exploratory laboratory evaluations related to vaccine research in general and for research assay validation. Genetic testing will not be

performed in this study, but may be performed on stored samples at later time as needed, in accordance with the genetic testing information that is included in the study informed consent.

8.6.2 Storage and Tracking of Blood Samples and Other Specimens

All of the stored study research samples are labeled by a code that only the site can link to the subject. Samples will be collected at sites and shipped in batches to Battelle where these samples will be kept in secure facilities with limited access.

Data will be kept in password-protected computers. Only investigators or their designees will have access to the samples and data. Samples will be tracked in the Laboratory Information Management System (LIMS) database or using another software designed for this purpose (e.g., Freezerworks).

8.6.3 Disposition of Samples, Specimens and Data at Completion of the Protocol

In the future, other investigators (both at NIH and outside) may wish to study these samples and/or data. IRB approval must be sought prior to any sharing of samples. Any clinical information shared about those samples would similarly require prior IRB approval. The research use of stored, unlinked or unidentified samples may be exempt from the need for prospective IRB review and approval. Exemption requests will be submitted in writing to the NIH Office of Human Subjects Research, which is authorized to determine whether a research activity is exempt.

At the time of protocol termination, samples will either remain in the contracted central repository, or IND Sponsor laboratories or, after IRB approval, samples may be transferred to another repository. Data will be archived by the IND Sponsor in compliance with requirements for retention of research records, or after IRB and the IND Sponsor approval, it may be either destroyed or transferred to another repository.

8.6.4 Loss or Destruction of Samples, Specimens or Data

Any loss or unanticipated destruction of samples (for example, due to freezer malfunction) or data (for example, misplacing a printout of data with identifiers) that compromises the scientific integrity of the study will be reported to the site IRB in accordance with institutional policies. The site PI will also notify the site IRB if the decision is made to destroy the remaining samples.

8.7 Subject Compensation

Subjects will be compensated for time and inconvenience of study participation in accordance with the site-specific IRB approved plan. The total compensation is included in the site-specific informed consent document.

8.8 Safety Monitoring

8.8.1 Protocol Safety Review Team

The site PI is responsible for ensuring daily review of the site's clinical safety data as it becomes available. The PSRT includes the IND Medical Officer or designee, the study Protocol Chairs, and the site PI or designee.

The PSRT will review the summary study safety data reports weekly from initiation of the study through 4 weeks after the last subject receives the last product administration, and will continue to monitor the safety data reports on a monthly basis through completion of the last study visit, in order to be certain that the investigational vaccine has an acceptable safety profile. The PSRT will be notified and convened to review any study pauses and to conduct safety reviews for a dose escalation.

9 ADMINISTRATIVE AND LEGAL OBLIGATIONS

9.1 Protocol Amendments and Study Termination

Protocol amendments must be made only with the prior approval of the IND Sponsor VRC, NIAID. Agreement from the site PI must be obtained for all protocol amendments and amendments to the ICF. All study amendments will be submitted to the IRB for approval.

The VRC Protocol Study Chairs, the site IRB, NIAID and the FDA reserve the right to terminate the study. The IND Sponsor will notify the site IRB in writing of the study's completion or early termination.

9.2 Study Documentation and Storage

The site PI will maintain a list of appropriately qualified persons to whom trial duties have been delegated.

Source documents are original documents, data, and records from which the subject's data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, radiographs, and correspondence.

The site PI and staff are responsible for maintaining a comprehensive and centralized filing system of all essential study-related (essential) documentation, suitable for inspection at any time by representatives from the VRC, IRB, FDA, and/or applicable regulatory authorities. Elements include:

- Subject files containing completed informed consent forms, and supporting copies of source documentation (if kept), and
- Study files containing the protocol with all amendments, IB, copies of all correspondence with the IRB and VRC

All essential documentation should be retained by the institution for the same period of time required for medical records retention. The FDA requires study records to be retained for up to two years after marketing approval or refusal (21 CFR 312.62). No study document should be destroyed without prior written agreement between the IND Sponsor, and the site PI. Should the investigator wish to assign the study records to another party or move them to another location, they must notify the IND Sponsor in writing of the new responsible person and/or the new location.

9.3 Data Collection and Protocol Monitoring

9.3.1 Data Collection

Clinical research data will be collected in a secure electronic web-based clinical data management system through a contract research organization, Emmes Corporation, Rockville, MD. Extracted data without patient identifiers will be sent to the Protocol Statistician for statistical analysis.

9.3.2 Data Sharing Plan

Data generated in this study will be shared as de-identified data in the government-funded public repository, www.ClinicalTrials.gov. Data may be shared prior to publication at approved public presentations or for collaborative development and will be shared at the time of publication or within 1 year of the primary completion date.

9.3.3 Source Documents

The site will maintain appropriate medical and research records for this trial, in compliance with International Conference on Harmonization – Good Clinical Practice (ICH-GCP), regulatory and institutional requirements for the protection of confidentiality of subjects.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, medical records, laboratory reports, pharmacy records and other research records maintained for the clinical trial.

9.3.4 Protocol Monitoring Plan

The VRC/NIAID or their authorized representatives are responsible for contacting and visiting the site investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the trial, provided that subject confidentiality is respected.

Site investigators will allow the study monitors, the site IRB, and the FDA to inspect study documents (*e.g.*, ICF, drug distribution forms, and case report forms) and pertinent hospital or clinic records for confirmation of the study data.

Site visits by study monitors will be made in accordance with the study monitoring plan to monitor the following: study operations, the quality of data collected in the research records, the accuracy and timeliness of data entered in the database, and to determine that all process and regulatory requirements are met. Study monitoring visits will occur as defined by the IND Sponsor approved monitoring plan.

9.4 Language

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

9.5 Policy Regarding Research-Related Injuries

The research site will provide short-term medical care for any injury resulting from participation in this research. In general, the NIH, the research site, or the Federal Government will provide no long-term medical care or financial compensation for research-related injuries.

9.6 Site Management

The IND Sponsor is responsible for overall study management. Assistance in managing the study is being provided by specific Sponsor representatives as per contractual obligations.

The site that will be enrolling and vaccinating study subjects will have a site PI. A PI is defined as an individual who actually conducts a clinical investigation at a study site and under whose immediate direction the study product is administered to subjects. The PI is required to conduct the study in compliance with all applicable regulations and good clinical practices.

The site will be required to obtain a local IRB approval for the protocol, all protocol amendments, and study supplementary documentation as per the site IRB requirements.

Publication of any study related information is governed by VRC, NIAID, NIH policies. Specifically, neither the CROs nor site personnel may submit for public presentation any meeting abstract or manuscripts without prior review by VRC.

10 REFERENCES

1. Griffin, D.E., *Alphaviruses*, in *Fields Virology*, D.M. Knipe and P.M. Howley, Editors., Lippincott Williams & Wilkins; 2007. p. 1023-67.
2. CDC, *Category A and B Biological Agents*. Public Health Preparedness: Mobilizing State by State, 2008.
3. Zacks, M.A. and S. Paessler, *Encephalitic alphaviruses*. *Veterinary Microbiology*, 2010. **140**(3-4): p. 281-286.
4. Dupuy, L.C. and D.S. Reed, *Nonhuman primate models of encephalitic alphavirus infection: historical review and future perspectives*. *Current Opinion in Virology*, 2012. **2**(3): p. 363-367.
5. Bale, J.F., Jr., *Viral encephalitis*. *Med Clin North Am*, 1993. **77**(1): p. 25-42.
6. Weaver, S.C. and W.K. Reisen, *Present and future arboviral threats*. *Antiviral Res*, 2010. **85**(2): p. 328-45.
7. Smith, D.W., J.S. Mackenzie, and S.C. Weaver, *Alphaviruses*, in *Clinical Virology, Third Edition*. 2009, American Society of Microbiology.
8. Akahata, W., et al., *A virus-like particle vaccine for epidemic Chikungunya virus protects nonhuman primates against infection*. *Nat Med*, 2010. **16**(3): p. 334-8.
9. Chang, L.J., et al., *Safety and tolerability of chikungunya virus-like particle vaccine in healthy adults: a phase 1 dose-escalation trial*. *Lancet*, 2014. **384**(9959): p. 2046-52.
10. Brewer, J.M., *(How) do aluminium adjuvants work?* *Immunol Lett*, 2006. **102**(1): p. 10-5.
11. Kuroda, E., C. Coban, and K.J. Ishii, *Particulate adjuvant and innate immunity: past achievements, present findings, and future prospects*. *Int Rev Immunol*, 2013. **32**(2): p. 209-20.
12. FDA. *Common Ingredients in U.S. Licensed Vaccines*. 2014; Available from: <http://www.fda.gov/biologicsbloodvaccines/safetyavailability/vaccinesafety/ucm187810.htm>.
13. He, P., Y. Zou, and Z. Hu, *Advances in aluminum hydroxide-based adjuvant research and its mechanism*. *Hum Vaccin Immunother*, 2015. **11**(2): p. 477-88.
14. Brito, L.A., P. Malyala, and D.T. O'Hagan, *Vaccine adjuvant formulations: a pharmaceutical perspective*. *Semin Immunol*, 2013. **25**(2): p. 130-45.
15. Brito, L.A. and D.T. O'Hagan, *Designing and building the next generation of improved vaccine adjuvants*. *J Control Release*, 2014. **190**: p. 563-79.
16. Schijns, V.E. and E.C. Lavelle, *Trends in vaccine adjuvants*. *Expert Rev Vaccines*, 2011. **10**(4): p. 539-50.
17. Oleszycka, E. and E.C. Lavelle, *Immunomodulatory properties of the vaccine adjuvant alum*. *Curr Opin Immunol*, 2014. **28**: p. 1-5.
18. Roldao, A., et al., *Virus-like particles in vaccine development*. *Expert Rev Vaccines*, 2010. **9**(10): p. 1149-76.
19. Roy, P. and R. Noad, *Virus-like particles as a vaccine delivery system: myths and facts*. *Hum Vaccin*, 2008. **4**(1): p. 5-12.
20. Pittman, P. and S.A. Plotkin, *Biodefence and Special Pathogen Vaccines*, in *Vaccines, 5th ed.*, S.A. Plotkin, W.A. Orenstein, and P.A. Offit, Editors., Elsevier; 2008: Philadelphia, PA. p. 1123-33.

21. Pittman, P.R., et al., *Long-term duration of detectable neutralizing antibodies after administration of live-attenuated VEE vaccine and following booster vaccination with inactivated VEE vaccine*. *Vaccine*, 1996. **14**(4): p. 337-43.
22. McClain, D.J., et al., *Immunologic interference from sequential administration of live attenuated alphavirus vaccines*. *J Infect Dis*, 1998. **177**(3): p. 634-41.
23. Calisher, C.H., D.R. Sasso, and G.E. Sather, *Possible evidence for interference with Venezuelan equine encephalitis virus vaccination of equines by pre-existing antibody to Eastern or Western Equine encephalitis virus, or both*. *Appl Microbiol*, 1973. **26**(4): p. 485-8.
24. Pittman, P.R., et al., *Immune interference after sequential alphavirus vaccine vaccinations*. *Vaccine*, 2009. **27**(36): p. 4879-82.
25. Reisler, R.B., et al., *Immune interference in the setting of same-day administration of two similar inactivated alphavirus vaccines: Eastern equine and western equine encephalitis*. *Vaccine*, 2012.
26. Clements, C.J. and E. Griffiths, *The global impact of vaccines containing aluminium adjuvants*. *Vaccine*, 2002. **20 Suppl 3**: p. S24-33.
27. Petrovsky, N. and J.C. Aguilar, *Vaccine adjuvants: current state and future trends*. *Immunol Cell Biol*, 2004. **82**(5): p. 488-96.
28. Baylor, N.W., W. Egan, and P. Richman, *Aluminum salts in vaccines--US perspective*. *Vaccine*, 2002. **20 Suppl 3**: p. S18-23.
29. Gupta, R.K., et al., *Adjuvant properties of aluminum and calcium compounds*. *Pharm Biotechnol*, 1995. **6**: p. 229-48.
30. Chackerian, B., *Virus-like particles: flexible platforms for vaccine development*. *Expert Rev Vaccines*, 2007. **6**(3): p. 381-90.

APPENDIX I: STUDY INFORMED CONSENT FORM

The template informed consent form is provided to guide development of a site-specific consent form. Only IRB-approved consent forms will be used to consent subjects for study participation.

Template: Study Informed Consent Form

STUDY TITLE: VRC 313

A Phase 1 Open Label, Dose-Escalation Clinical Trial to Evaluate the Safety and Immunogenicity of a Trivalent Virus-Like Particle (VLP) Encephalitis Vaccine, VRC WEVLP073-00-VP, in Healthy Adults.

INTRODUCTION

We invite you to take part in a research study at the [Insert Site name here]

The study is sponsored by the National Institutes of Health (NIH) in Bethesda, MD, USA. You can decide if you want to take part in this study or not. There is no penalty or loss of benefits if you choose not to take part. Please ask questions and talk about this study with anyone you want. Take as much time as you need to decide. You will be given a copy of this consent form.

SCREENING

Before you can take part in this experimental study, your health will be checked so we can decide if you qualify to participate. You will need to sign this consent form before screening. If you qualify, then you may take part in the vaccine study.

Screening includes a physical exam and blood tests to check your health. We will ask you about your health history. If you are a female who is able to have children, you will be asked about the possibility of you becoming pregnant while in the study. You will be tested for pregnancy and for HIV. During screening, we will collect some blood to store for research. We will review the test results with you and tell you if the results show that you are eligible to join the study.

PURPOSE OF THE STUDY

This is the first study in people of this experimental vaccine for the prevention of Western equine encephalitis virus, Eastern equine encephalitis virus, and Venezuelan equine encephalitis virus infection. The word “Encephalitis” means swelling of the brain, which occurs in some people who get infected by these viruses. “Experimental” means that the Food and Drug Administration (FDA) has not approved this study vaccine for general use in the public. The FDA allows it to be used for research only. We do not know if this vaccine works. The main purpose of this study is to see if the experimental vaccine is safe and if there are any side effects. We also want to study the immune response to this vaccine.

BACKGROUND

These 3 viruses were first seen in horses, that’s why they were named “equine”. Western, Eastern and Venezuelan equine encephalitis viruses are very similar to each other and cause a similar type of disease in humans. The viruses are passed to humans by mosquitoes. Infection from these viruses can cause fever, chills, discomfort, feeling sick, muscle pain and then headache, vomiting, restlessness, irritability, seizures, coma and death.

STUDY PRODUCTS

Vaccines are given to teach the body to prevent or fight an infection. In this study, we are testing an experimental vaccine that was developed by the Vaccine Research Center (VRC) at the NIH. It is named VRC-WEVVLP073-00-VP, but is also called the “WEVEE” vaccine. This vaccine is intended to help the body to make an immune response to Western, Eastern and Venezuelan equine encephalitis viruses.

The WEVEE vaccine: Most vaccines are made of proteins that are injected into a muscle. Proteins are natural substances that the body and viruses use as building blocks. The WEVEE vaccine is a type of vaccine known as a virus-like particle (VLP) vaccine. This is because it is made up of proteins from the Western, Eastern and Venezuelan equine encephalitis viruses that make particles that look like the outside surface of these 3 viruses. The body’s immune system may respond to these particles by making cells to fight off these viruses.

However, there are no live or killed viruses in the vaccine, so you cannot get infected with any of these 3 viruses from getting the vaccine. This is the first study to give the WEVEE vaccine to humans. You should not expect this experimental vaccine to protect you from Western, Eastern and Venezuelan equine encephalitis viruses infection.

Some people in this study will get the WEVEE vaccine mixed with another study product called an adjuvant.

Adjuvants are substances that may make your body’s response to the vaccine better. The adjuvant in this study will be aluminum hydroxide (alum). Alum has been used for over 60 years in billions of vaccinations with licensed vaccines and has been found to be safe. The use of alum as an adjuvant in this study has been reviewed and approved by the FDA.

ELIGIBILITY

You are eligible to take part in this study if you are:

- between 18 and 50 years of age
- in general good health without significant medical problems
- willing to get the WEVEE vaccine
- willing to give blood samples for future research
- additionally, if you are a female who is able to become pregnant: willing to use birth control from at least 21 days before randomization through the end of the study

STUDY PLAN

About 30 people will take part in this study. You will be in the study for about 36 weeks (8 months) and have about 9 clinic visits and 2 telephone contacts. You will get 2 vaccinations, each by injection (shot) in the upper arm muscle. This is called an intramuscular “IM” injection. We will check you for any side effects from the vaccine.

We will tell you if we learn anything new during this study that might cause you to change your mind about staying in the study. At the end of the study, we will tell you when study results may be available and how to learn about them.

If you agree to take part in the study, you will be randomly assigned (like pulling a number from a hat) to get either:

- The WEVEE vaccine alone (Group 1, Group 3, and Group 5) or,
- The WEVEE vaccine mixed with alum (Group 2, Group 4, and Group 6).

Once enrolled, you will know which group you are in.

The study will start by randomizing people to get a dose of 6 mcg in Group 1 or Group 2. We will review the data after about 2 weeks to make sure this vaccine dose has no safety concerns before we start randomizing people to get the next dose of 30 mcg in Group 3 or Group 4. We will review the data for this dose after about 2 weeks to make sure this vaccine dose has no safety concerns before we start randomizing people to the 60 mcg dose in Group 5 or Group 6.

The table below shows the vaccination plan:

VRC 313				
Group	Subjects	Dose	Day 0	Week 8
1	5	6 mcg	WEVEE	WEVEE
2	5		WEVEE + alum	WEVEE + alum
3	5	30 mcg	WEVEE	WEVEE
4	5		WEVEE + alum	WEVEE + alum
5	5	60 mcg	WEVEE	WEVEE
6	5		WEVEE + alum	WEVEE + alum
Total	30			

STUDY PROCEDURES

Each vaccination visit will take about 4 to 6 hours. Other clinic visits will take about 1 to 2 hours. The clinic staff will watch you for at least 30 minutes after each vaccination.

If you are a woman who is able to get pregnant, we will do a pregnancy test before each injection. The test must show that you are not pregnant to get the injection.

You will have a telephone call about 2 days after each vaccination so we can check on you.

You will need to complete a diary card at home for 7 days after each vaccination. The purpose of the diary card is so you can write down any symptoms that the vaccine may cause. We will ask you to record your temperature daily and look at the injection site on your arm each day. We will give you a thermometer to measure your temperature and a ruler to measure any skin changes at the injection site. You will get a password to a secure website to enter this data online. If you do not have access to the internet, you may use a paper diary card instead.

If you have any side effects, you should tell a clinic nurse or doctor as soon as possible. You can reach the staff by phone 24 hours a day. If you have symptoms, you may be asked to come to the clinic for an examination before your next scheduled visit. With your consent, we may take a photograph of any reactions you have to the vaccine. It is very important that you follow the instructions from the clinic staff.

At each visit, we will check you for any health changes or problems. We will ask you how you are feeling and if you have taken any new medications. We will draw your blood at each visit, taking up to 5 tubes of blood. We will tell you right away if any of your test results show a

health problem. Some blood samples will be used for research only, to study your immune response to the vaccine. Results of these research tests are not used to check your health and will not be given to you.

MONITORING OF THE STUDY

This study will be monitored by a group of physicians and scientists associated with the NIH. This group will review the study information and will pay close attention to any reactions. If there are serious side effects, study injections may be delayed or canceled.

Your research study charts may be reviewed by the IND Sponsor representatives.

GENETIC TESTING

Some genetic tests are done in research studies to see if genetic differences in people cause different types of immune responses. Genetic testing will not be done in this study, but may be performed on stored samples at later time. If genetic tests are done at a later time, your name and identifying information will not be on your samples and the results will not be in your medical record. These tests are not used to check your health and we will not tell you the results.

STORED SAMPLES

Some of the blood we draw from you during the study will be used by investigators to study proteins and other molecules that may be involved in the immune response. Blood samples will be stored for future research to learn more about WEVEE, vaccines, the immune system, and/or other medical conditions.

The results from the research done with your stored samples are not meant to be used for medical care. They will not be given to your health care provider and will not be put in your medical record.

You may not take part in this study if you are not willing to have your blood samples stored for future analysis.

Labeling of Stored Samples: Your stored samples will be labeled by a special code or number and not your personal information. Only the study team can link this code to you. Any identifying information about you (like name or date of birth) will be kept as confidential as allowable by law.

Risks from Stored Samples: There is a risk of unplanned release of information from your medical records. The chance that this information will be given to an unauthorized person without your permission is very small. Possible problems with the unplanned release of information include discrimination when applying for insurance or employment. Similar problems may occur if you give information yourself or agree to have your medical records released.

Future Studies: In the future, other investigators at NIH or outside of NIH may wish to study your stored samples. When the study team shares your stored samples, they will be marked with a code, but will not have any identifying information on them. Some information about you, like your gender, age, health history, or ethnicity may also be shared with other researchers. Any

future research studies using your samples will be conducted in a way that protects the rights and privacy of study participants.

Your stored samples will be used only for research and will not be sold. The research done with your samples may be used to make new products in the future, but you will not get payment for such products.

Making your Choice: You cannot take part in this study if you do not want us to collect or store your blood samples. If you agree to take part in this study, you must also agree to let us keep any of your samples for future research.

HUMAN DATA SHARING

To advance science, it is helpful for researchers to share information they get from studying humans by putting it into shared scientific databases. Researchers can then study the information combined from many studies to learn even more about health and diseases.

If you agree to take part in this study, some of your data will be placed into one or more scientific databases. We will remove identifying information like your name, address, and birth date. The data may then be used for future research and shared broadly for research purposes. Only researchers who are approved to access the database may be able to see and use your information. You will not get any direct benefits from future research that uses your data and information.

POSSIBLE STUDY RISKS

Possible risks of injections: Temporary stinging, pain, redness, soreness, itchiness, swelling, bruising, or a cut in the arm. There is a very small chance of infection.

Possible risks of any vaccine: Fever, chills, rash, aches and pains, nausea, headache, dizziness, and feeling tired and/or unwell. These reactions are usually greatest within the first 24 hours after vaccination and typically last 1 to 3 days. Over-the-counter medicine, like acetaminophen (Tylenol) or ibuprofen, may be used to help relieve these symptoms.

Very rarely, a serious allergic reaction may occur shortly after any vaccination. This is called “anaphylaxis” and may be life-threatening. While you are waiting in the clinic after the vaccination, we will watch you for anaphylaxis. Treatment for anaphylaxis will be given right away if it occurs.

Possible risks of blood drawing: Pain, bleeding, bruising, feeling lightheaded, fainting, or rarely, infection at the site where the blood is taken.

Possible risks of WEVEE Vaccine: The WEVEE vaccine has not been given to people before and it may have unknown risks or side effects. It has been tested in mice and monkeys. The vaccine did not have any severe side effects and met the safety criteria to be tested in humans. In a study of a similar product, a chikungunya virus VLP vaccine was well tolerated with no reported joint pain or fever after vaccination. No serious adverse events were reported.

Possible risk of aluminum hydroxide suspension: Aluminum adjuvants have been found to be safe for over 60 years. Aluminum-containing vaccines have been associated with reactions of the skin (erythema), bumps in the skin (subcutaneous nodules), contact hypersensitivity and small nodular skin lesions.

Possible risks during Pregnancy: We do not know the possible effects of the study vaccines on a fetus or nursing infant. Women who are able to become pregnant must have a negative pregnancy test before each study injection and agree to practice adequate birth control beginning at least 21 days before getting the first injection until the last study visit. If you are pregnant, breast-feeding or want to become pregnant during the next 36 weeks, you cannot take part.

You must also tell the clinic if you think that you are or might be pregnant during this study. If you become pregnant, you will not get any more injections. However, you will be asked to continue with follow-up visits so we can check your health. You will also be asked about the outcome of your pregnancy.

Possible other risks: The safety of the vaccine tested in this study is unknown. It is unknown if the study injection will affect how you respond to any future infection with WEVEE or to any other WEVEE vaccines that you may get in the future.

You may not donate blood at a blood bank while taking part in this study. You may not donate blood for one year after your last study injection.

POSSIBLE BENEFITS

This study is not designed to benefit you or protect you from infection from these viruses. Others may benefit in the future from the information that will be learned from the study.

COSTS TO YOU FOR YOUR PARTICIPATION

There are no costs to you for taking part in this study. We will not charge you or your insurance carrier for any health evaluations or services. You or your health insurance will have to pay for all costs for medical care that you get outside this study. It is possible that you may have some costs that are not covered by the study compensation we give you.

COMPENSATION TO YOU FOR YOUR PARTICIPATION

You will be compensated for your time and inconvenience as follows: [insert site plan]. This will be based on the number of study visits you attend and study injections you get.

Actual compensation is based on the number and type of study visits you finish. Your compensation may need to be reported to the Internal Revenue Service (IRS) as taxable income.

REASONS FOR REMOVING YOU FROM THE STUDY WITHOUT YOUR CONSENT

The study doctor can take you out of this study without your consent if:

- You don't keep appointments or follow study procedures.
- You get a serious illness that needs ongoing medical care.
- You need to get treatment with a medication that affects your immune system (such as a steroid like prednisone)
- You enroll in another research study at the same time you are in this study.
- You become pregnant.
- The study is stopped by regulatory agencies, the study sponsor or study investigators. If this happens, we will tell you why.

If you agree to take part in this study, it is important for you to keep all of your appointments.

Your participation in this study is completely voluntary. You can choose to stop taking part in the study at any time. There is no penalty or loss of benefits for choosing to leave the study.

If you get the first injection but not the second, we still want you to continue with all planned follow-up visits until the end of the study. It is important that we continue to check your health even if you do not get the second vaccination.

ALTERNATIVES

This study is not designed to treat or prevent any disease. You may choose not to take part in this study. You may be eligible for other studies.

CONFLICT OF INTEREST

[Insert site specific COI information].

The NIH developed the investigational product being used in this research study. The results of this study could play a role in whether the FDA will approve the study product for sale at some time in the future. If approved, the future sale of the study product could lead to payments to NIH and some NIH scientists. By U.S. law, government scientists are required to get such payments for their inventions. You will not get any money from the development or sale of the product.

CLINICALTRIALS.GOV

A description of this clinical trial will be available on www.ClinicalTrials.gov. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

APPENDIX II: CONTACT INFORMATION

APPENDIX III: SCHEDULE OF EVALUATIONS

		Screen	VRC 313 Schedule of Evaluations									
Visit		*01	02	02A	03	04	05	05A	06	07	08	09
Week of Study		-4 to 0	W1	W1	W2	W4	W8	W9	W10	W12	W24	W36
Day of Study		-28 to 0	D0 ¹	D2	D14	D28	D56	D58	D70	D84	D168	D252
Clinical	Tube											
VRC 313 Informed Consent		X										
VRC 313 AoU		X										
² Physical exam for eligibility, height /weight /vital signs and targeted exam (as needed) at other visits.		X	X		X	X	X		X	X	X	X
Medical history targeted to eligibility at screening; then interim medical history		X	X		X	X	X		X	X	X	X
³ Study product administration			X				X					
Phone evaluation (clinic visit as needed)				X				X				
Begin 7-Day Diary Card			X				X					
⁴ Pregnancy test: urine (or serum)		X	X				X				X	
Counseling on pregnancy prevention/ Reproductive Information Form		X	X		X	X	X		X	X	X	X
CBC, differential, platelet count	EDTA	3	3		3	3	3		3	3	3	3
ALT	SST	4	4		4	4	4		4	4	4	4
Creatinine	SST	X	X				X					
HIV ELISA (Western blot or PCR, if needed)	SST	4										
Research												
Antibody assays and serum	SST	*16	32		16	32	32		16	32	16	16
Daily Volume (mL)		27	39	0	23	39	39	0	23	39	23	23
Max. Cumulative Volume (mL)		27	66	66	89	128	167	167	190	229	252	275

* Screening: Most screening evaluations must be no more than 28 days prior to Day 0 to be used for eligibility (pregnancy test on Day 0 must be used for eligibility). If clinical assessment on Day 0 suggests significant changes may have occurred since screening, then physical examination and laboratory studies done on Day 0 are used for eligibility.

¹ Day 0=day of randomization and first product administration. Day 0 evaluations prior to first product administration are the baseline for assessing adverse events subsequently.

² Screening visit includes a physical exam with vital signs. At other visits a physical examination is done if indicated by interim history or laboratory test results. Otherwise only blood pressure (BP), pulse, and temperature are required.

³ Study product administrations: Complete post vaccination evaluations (BP, pulse, temperature, respiration and product administration site assessment) at 30 minutes or longer after each product administration. Subjects who receive only one product administration are expected to continue with follow-up through study Week 36.

⁴ Negative pregnancy test results must be confirmed for women of reproductive potential prior to product administrations.

Visit Windows: Schedule Visits 02A through 05 with respect to Day 0; Schedule Visits 05A through 9 with respect to Visit 05.

The following visit windows apply: Visits 02A and 05A (+1 day). Visits 03 and 06 (±3 day). Visits 04 and 07 (±7 days). Visit 05 (± 7 days). Visits 08 and 09 (±14 days).

**APPENDIX IV: ASSESSMENT OF RELATIONSHIP TO VACCINE
AND
GRADING SEVERITY OF ADVERSE EVENTS**

Assessment of Causality Relationship of an Adverse Event to Study Vaccine:

The relationship between an adverse event (AE) and the vaccine will be assessed by the investigator on the basis of his or her clinical judgment and the definitions below.

Definitely Related. The AE and administration of study agent are related in time, and a direct association can be demonstrated.

Probably Related. The AE and administration of study agent are reasonably related in time, and the AE is more likely explained by study agent than other causes.

Possibly Related. The AE and administration of study agent are reasonably related in time, but the AE can be explained equally well by causes other than study agent.

Not Related. There is not a reasonable possibility that the AE is related to the study agent.

For purposes of preparing data reports in which AE attributions are limited to “**Related**” or “**Not Related**”, in this protocol, the “**Definitely, Probably and Possibly**” attributions will be mapped to the “**Related**” category. The definitions that apply when these two categories alone are used are as follows:

Related – There is a reasonable possibility that the AE may be related to the study agent.

Not Related – There is not a reasonable possibility that the AE is related to the study agent.

Grading the Severity of Adverse Events:

The FDA Guidance for Industry (September 2007): “Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials” is the basis for the severity grading of AEs in this protocol. Several modifications were made to the table as follows:

“Emergency room visit” is not automatically considered a life-threatening event; these words have been removed from any “grade 4” definition where they appear in the table copied from the guidance document.

Any laboratory value shown as a “graded” value in the table that is within the institutional normal range will not be severity graded or recorded as an AE.

Severity grading for hemoglobin decrease on the basis of the magnitude of decrease from baseline is not applicable at the grade 1 level; only absolute hemoglobin will be used to define grade 1 decrease. Increases in hemoglobin are AEs only for values above the upper limit of normal and are graded by the systemic illness clinical criteria.

Severity grading definition for Grade 4 local reaction to injectable product (Erythema/Redness and Induration/Swelling) included added text “requiring medical attention”.

1 X ULN was removed from the definition for PT increase.

When not otherwise specified in the table, the following guidance will be used to assign a severity grade:

Grade 1 (Mild): No effect on activities of daily living

Grade 2 (Moderate): Some interference with activity not requiring medical intervention

Grade 3 (Severe): Prevents daily activity and requires medical intervention

Grade 4 (Life-threatening): Hospitalization; immediate medical intervention or therapy required to prevent death.

Grade 5 (Death): Death is assigned a Grade 5 severity.

Only the single AE that is assessed as the primary cause of death should be assigned “grade 5” severity.

**Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in
 Preventive Vaccine Clinical Trials
 FDA Guidance - September 2007**

A. Tables for Clinical Abnormalities

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	Hospitalization
¹ Erythema/Redness	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis requiring medical attention
² Induration/Swelling	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis requiring medical attention
³ Vital Signs				
	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
⁴ Fever (°C) (°F)	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	Hospitalization for arrhythmia
⁵ Bradycardia - beats per Minute	50 – 54	45 – 49	< 45	Hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155	Hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	Hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	Hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

1. In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.
2. Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.
3. Subject should be at rest for all vital sign measurements.
4. Oral temperature; no recent hot or cold beverages or smoking.
5. When resting heart rate is between 60 – 100 beats per minute. Use clinical judgment when characterizing Bradycardia among some healthy subject populations, for example, conditioned athletes.

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Nausea/vomiting	No interference with activity or 1 – 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	Hospitalization for hypotensive shock
Diarrhea	2 – 3 loose stools or < 400 gms/24 hours	4 – 5 stools or 400 – 800 gms/24 hours	6 or more watery stools or > 800gms/24 hours or requires outpatient IV hydration	Hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	Hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	Hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	Hospitalization

Systemic Illness	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	Hospitalization

B. Tables for Laboratory Abnormalities

The laboratory values provided in the tables below serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

Serum*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6

Serum*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL	100 – 110 110 – 125	111 – 125 126 – 200	>125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	≥ 3.1 – 10 x ULN	> 10 x ULN
Liver Function Tests – ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example, a low sodium value that falls within a grade 3 parameter (125-129 mEq/L) should be recorded as a grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.

***ULN” is the upper limit of the normal range.

Hematology*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) decrease from baseline value - gm/dL	not applicable	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) decrease from baseline value – gm/dL	not applicable	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm ³	10,800 – 15,000	15,001 – 20,000	20,001 – 25,000	> 25,000
WBC Decrease - cell/mm ³	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm ³	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm ³	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm ³	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm ³	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT – increase by factor (prothrombin time)	1.10 x ULN**	1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	> 1.25 ULN
PTT – increase by factor (partial thromboplastin time)	1.10 – 1.20 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.



Date: March 12, 2019
RE: Letter of Amendment #1
Protocol VRC 313, Version 1.0 (January 9, 2019)
To: Emory University Institutional Review Board
From: Srilatha Edupuganti, M.D., MPH, Principal Investigator

Letter of Amendment #1

This Letter of Amendment (LoA) affects the VRC 313, Version 1.0 (January 9, 2019). This letter and any IRB correspondence pertaining to this letter will be filed in the protocol regulatory file and other pertinent files.

Purpose of the Letter of Amendment

The purpose of this LoA is to update the protocol as described below. New text is shown in **bold**, deleted text in ~~strikethrough~~.

1. Title page

Correct a typo in the IND number as follows: BB-IND ~~44738~~**17338**

2. Section 4.1, Inclusion Criteria

Clarify inclusion criterion #9 as follows: “White blood cell (WBC) **and** differential either within institutional normal range or accompanied by PI or designee approval”

3. Section 4.2.2, Screening

Since a witness signature on the ICF is not required, the following text is to be modified as follows: “Before screening procedures can be performed, informed consent must be obtained, and the form must be signed, dated and timed by the subject as well as signed and dated by the consentor ~~and a witness. Any member of the research/clinical team can be a witness, but a consentor and a witness should not be the same person at the same time.~~”

4. Section 4.2, Clinical Procedures and Evaluations

Add a new sub-section “*Birth Control*” to clarify that:

- **Adequate methods of reversible/temporary birth control for women generally include: abstinence; condoms, male or female, with or without a spermicide; diaphragm or cervical cap with spermicide; intrauterine devices and other prescription methods (such as contraceptive pills, hormone implants, injections, patches and others); or a male partner who has previously undergone a vasectomy.**
- **Permanent birth control for women includes:**
 - **Hysterectomy or partial hysterectomy are both forms of permanent birth control**
 - **Tubal ligation or Essure implant: FDA has prevented sales of Essure in the U.S. since Dec. 2018, but health care providers may continue to implant current devices for 1 year from date of purchase if they review the black box warning and “Patient-Doctor Discussion Checklist” with the patient.**

- **Menopausal (menses ceased for at least 1 year and no other biological or physiological cause in medical history)**

Women who have permanent birth control do not need pregnancy testing.

5. *Appendix I, Study Informed Consent Form Template*

- Under “Study Plan” clarify that the length of the study is 9 months as follows: “You will be in the study for about 36 weeks (& 9 months) and have about 9 clinic visits and 2 telephone contacts.”
- Remove the signature line for witness

6. *Appendix II, Contact Information*

- [REDACTED]

7. *Appendix III, Schedule of Evaluations*

- Clarify that HIV testing will be done per institutional guidelines by HIV antibody (Ab)/antigen (Ag) combination assay using 5 ml of blood
- The Schedule of Evaluations with updated blood Daily Volume and Max. Cumulative Volume (blood volumes increased by 1 mL) is attached

No changes to the to the study conduct, subject’s risks and to content of the informed consent are indicated based on this LoA.

The changes described herein will be incorporated into the next version of protocol VRC 313 if amended in the future.

Also with this LoA, we submit for approval a modified Assessment of Understanding (AoU) to which we added a line to indicate the time when the AoU was conducted.

		Screen	VRC 313 Schedule of Evaluations									
Visit		*01	02	02A	03	04	05	05A	06	07	08	09
Week of Study		-4 to 0	W1	W1	W2	W4	W8	W9	W10	W12	W24	W36
Day of Study		-28 to 0	D0 ¹	D2	D14	D28	D56	D58	D70	D84	D168	D252
Clinical												
VRC 313 Informed Consent	Tube	X										
VRC 313 AoU		X										
² Physical exam for eligibility, height /weight /vital signs and targeted exam (as needed) at other visits.		X	X		X	X	X		X	X	X	X
Medical history targeted to eligibility at screening; then interim medical history		X	X		X	X	X		X	X	X	X
³ Study product administration			X				X					
Phone evaluation (clinic visit as needed)				X				X				
Begin 7-Day Diary Card			X				X					
⁴ Pregnancy test: urine (or serum)		X	X				X				X	
Counseling on pregnancy prevention/ Reproductive Information Form		X	X		X	X	X		X	X	X	X
CBC, differential, platelet count	EDTA	3	3		3	3	3		3	3	3	3
ALT	SST	4	4		4	4	4		4	4	4	4
Creatinine	SST	X	X				X					
HIV Ab/Ag Combo (other tests, if needed)	SST	5										
Research												
Antibody assays and serum	SST	*16	32		16	32	32		16	32	16	16
Daily Volume (mL)		28	39	0	23	39	39	0	23	39	23	23
Max. Cumulative Volume (mL)		28	67	67	90	129	168	168	191	230	253	276

Date: October 24, 2019
RE: Letter of Amendment #3
Protocol VRC 313, Version 1.0 (January 9, 2019)
To: Emory University Institutional Review Board
From: Srilatha Edupuganti, M.D., MPH, Principal Investigator

Letter of Amendment #3

This Letter of Amendment (LoA) affects the VRC 313, Version 1.0 (January 9, 2019). This letter and any IRB correspondence pertaining to this letter will be filed in the protocol regulatory file and other pertinent files.

Purpose of the Letter of Amendment

The purpose of this LoA is to update the protocol as described below. New text is shown in **bold** in the “in the *Schedule of Evaluations*.”

1. “*Appendix III: Schedule of Evaluations*”
 - Add collection of PBMC and plasma for exploratory immunogenicity evaluations at either Visit 08 or Visit 09 for all subjects enrolled in Groups 3-6 that have not yet completed Visit 08 or 09
 - Update the collection of blood and volume at Visits 8 or Visit 9 from 16mL SST tube to:
 - 8 ml for antibody assays and serum in SST tube
 - 8 ml for PBMC and plasma in CPT tube
 - No extra blood will be collected for any subject at Visits 8 or Visit 9, and the daily volume and max. cumulative volume remains the same.

No changes to the study conduct, subject’s risks and to content of the informed consent are indicated based on this LoA.

The changes described herein will be incorporated into the next version of protocol VRC 313 if amended in the future.

		Screen	VRC 313 Schedule of Evaluations									
Visit		*01	02	02A	03	04	05	05A	06	07	08	09
Week of Study		-4 to 0	W1	W1	W2	W4	W8	W9	W10	W12	W24	W36
Day of Study		-28 to 0	D0 ¹	D2	D14	D28	D56	D58	D70	D84	D168	D252
Clinical	Tube											
VRC 313 Informed Consent		X										
VRC 313 AoU		X										
² Physical exam for eligibility, height /weight /vital signs and targeted exam (as needed) at other visits.		X	X		X	X	X		X	X	X	X
Medical history targeted to eligibility at screening; then interim medical history		X	X		X	X	X		X	X	X	X
³ Study product administration			X				X					
Phone evaluation (clinic visit as needed)				X				X				
Begin 7-Day Diary Card			X				X					
⁴ Pregnancy test: urine (or serum)		X	X				X				X	
Counseling on pregnancy prevention/ Reproductive Information Form		X	X		X	X	X		X	X	X	X
CBC, differential, platelet count	EDTA	3	3		3	3	3		3	3	3	3
ALT	SST	4	4		4	4	4		4	4	4	4
Creatinine	SST	X	X				X					
HIV ELISA (Western blot or PCR, if needed)	SST	4										
Research												
Antibody assays and serum	SST	*16	32		16	32	32		16	32	16 [8] ⁵	16 [8] ⁵
⁵ PBMC and plasma	CPT										[8] ⁵	[8] ⁵
Daily Volume (mL)		27	39	0	23	39	39	0	23	39	23	23
Max. Cumulative Volume (mL)		27	66	66	89	128	167	167	190	229	252	275

* Screening: Most screening evaluations must be no more than 28 days prior to Day 0 to be used for eligibility (pregnancy test on Day 0 must be used for eligibility). If clinical assessment on Day 0 suggests significant changes may have occurred since screening, then physical examination and laboratory studies done on Day 0 are used for eligibility.

¹ Day 0=day of randomization and first product administration. Day 0 evaluations prior to first product administration are the baseline for assessing adverse events subsequently.

² Screening visit includes a physical exam with vital signs. At other visits a physical examination is done if indicated by interim history or laboratory test results. Otherwise only blood pressure (BP), pulse, and temperature are required.

³ Study product administrations: Complete post vaccination evaluations (BP, pulse, temperature, respiration and product administration site assessment) at 30 minutes or longer after each product administration. Subjects who receive only one product administration are expected to continue with follow-up through study Week 36.

⁴ Negative pregnancy test results must be confirmed for women of reproductive potential prior to product administrations.

Visit Windows: Schedule Visits 02A through 05 with respect to Day 0; Schedule Visits 05A through 9 with respect to Visit 05.

The following visit windows apply: Visits 02A and 05A (+1 day). Visits 03 and 06 (±3 day). Visits 04 and 07 (±7 days). Visit 05 (± 7 days). Visits 08 and 09 (±14 days).

⁵**PBMC and plasma collection for all subjects enrolled in Groups 3-6 that have not yet completed Visit 08 or Visit 09.**

ONLY draw 8 mL in SST (DO NOT draw 16 ml in SST tubes IF collecting PBMC and plasma).

You Are Being Asked to Be in a Research Study

Concise presentation of key concepts

You are being asked to be in a research study. A research study is designed to answer a scientific question. If you agree and are eligible to be in the study, you will be one of up to 40 people who are participating in this study at Emory.

Why is this study being done?

This study is being done to answer the questions: Is the WEVEE vaccine safe and tolerable to give people? Is it safe and tolerable at all three different dose levels? Is it safe and tolerable both with and without adding aluminum hydroxide (alum) to the vaccine? You are being asked to be in this research study because you are between the ages of 18 and 50 and are in generally good health.

Do you have to be in the study?

It is your decision to be part of this research study. You do not have to be in it. Before you make your decision, you should take time to learn about the study.

What do I have to do if I choose to participate in this study?

If you are eligible and want to participate in the study, you will participate for 9 months (9 study visits). The researchers will ask you to do the following: receive 2 vaccinations, provide information about your medical history, current medications and current health, have blood samples drawn and keep a symptom diary after each injection. ALL study procedures will be paid for by the study.

Is this study going to help you?

This study is not designed to benefit you directly. If you are in the study, you will be helping the researchers answer the study questions.

What are the risks or discomforts I should know about before making a decision?

The study will take time. The vaccine that is being tested may not work and may even cause harm. All studies have some risks. Some risks are relatively small, like being bored or losing time. Some are more serious – for this study, these include irritation at the injection site, allergic reaction, flu-like symptoms, loss of privacy, and breach of confidentiality. A full list of expected risks, their frequency and severity are in the “What are the possible risks and discomforts?” section of this document.

Alternatives to Joining This Study

You may choose not to participate in this study. If you do choose to participate, you may change your mind and withdraw from the study at any time.

Costs

You WILL NOT have to pay for any of the study procedures.

What Should I Do Next?

Read this form or have it read to you. Make sure the study doctor or study staff explains the study to you. Ask questions (e.g., about exact time commitment, about unfamiliar words, more details on specific procedures, etc.) Make sure you understand. Take time to consider this and talk about it with your family and friends.

Emory University
Consent to be a Research Subject

Title: A Phase 1 Open Label, Dose-Escalation Clinical Trial to Evaluate the Safety and Immunogenicity of a Trivalent Virus-Like Particle (VLP) Encephalitis Vaccine, VRC WEV/VLP073-00-VP, in Healthy Adults

Principal Investigator: Srilatha Edupuganti, MD, MPH

Sponsor: The Vaccine Research Center (VRC) and the National Institute of Allergy and Infectious Disease (NIAID)

Introduction

You are being asked to be in a medical research study. This form is designed to tell you everything you need to think about before you decide if you want to be a part of the study. **It is entirely your choice. If you decide to take part, you can change your mind later on and withdraw from the research study.** The decision to join or not join the research study will not cause you to lose any medical benefits. If you decide not to take part in this study, you can still receive medical care at Emory.

Before making your decision:

- Please carefully read this form or have it read to you
- Please listen to the study doctor or study staff explain the study to you
- Please ask questions about anything that is not clear

You can take a copy of this consent form, to keep. Feel free to take your time thinking about whether you would like to participate. You may wish to discuss your decision with family or friends. Do not sign this consent form unless you have had a chance to ask questions and get answers that make sense to you. By signing this form, you will not give up any legal rights.

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. law. This Web site will not include information that can identify you. At most the Web site will include a summary of the study results. You can search this Web site at any time.

What is the purpose of this study?

The purpose of this study is to test an experimental vaccine against viral encephalitis. This is the first study in people of this experimental vaccine for the prevention of Western equine encephalitis virus, Eastern equine encephalitis virus, and Venezuelan equine encephalitis virus infection. The word "Encephalitis" means swelling of the brain, which occurs in some people who get infected by these viruses. "Experimental" means that the Food and Drug Administration (FDA) has not approved this study vaccine for general use in the public. The FDA allows it to be used for research only. We do not know if this vaccine works. The main purpose of this study is to see if the experimental vaccine is safe and if there are any side effects. We also want to study the immune response to this vaccine.

Western, Eastern and Venezuelan equine encephalitis viruses are very similar to each other and cause a similar type of disease in humans. These 3 viruses were first seen in horses; that's why they were named "equine". The viruses are passed to humans by mosquitoes. Infection from these viruses can cause fever, chills, discomfort, feeling sick, muscle pain and then headache, vomiting, restlessness, irritability, seizures, coma, and death. There are no viruses in the vaccine, and therefore you can't get infected by the vaccine.

We expect that 30-40 people will receive a vaccine on this study. In order to find enough people, we may screen up to 120 people.

What is the vaccine being used in this study?

Vaccines are given to teach the body to prevent or fight an infection. In this study, we are testing an experimental vaccine that was developed by the Vaccine Research Center (VRC) at the National Institutes of Health (NIH). It is named VRC-WEVVLP073-00-VP; it is also called the “WEVEE” vaccine. This vaccine is intended to help the body to make an immune response to Western, Eastern and Venezuelan equine encephalitis viruses.

The WEVEE vaccine: Most vaccines are made of proteins that are injected into a muscle. Proteins are natural substances that the body and viruses use as building blocks. The WEVEE vaccine is a type of vaccine known as a virus-like particle (VLP) vaccine. This is because it is made up of proteins from the Western, Eastern and Venezuelan equine encephalitis viruses that make particles looking like the outside surface of these 3 viruses. The body’s immune system may respond to these particles by making cells to fight off these viruses.

However, there are no live or killed viruses in the vaccine, so you cannot get infected with any of these 3 viruses from getting the vaccine. This is the first study to give the WEVEE vaccine to humans. This experimental vaccine may or may not protect you from Western, Eastern and Venezuelan equine encephalitis viruses’ infection.

Some people in this study will get the WEVEE vaccine mixed with another study product called an adjuvant. Adjuvants are substances that may make your body’s response to the vaccine better. The adjuvant in this study will be aluminum hydroxide (alum). Alum has been used for over 60 years in billions of vaccinations with licensed vaccines and has been found to be safe. The use of alum as an adjuvant in this study has been reviewed and approved by the FDA.

Who can take part in this study?

You may be eligible to take part in this study if you are:

- between 18 and 50 years of age
- in general good health without significant medical problems
- willing to get the WEVEE vaccine
- willing to give blood samples for future research
- Additionally, if you are a female who is able to become pregnant: willing to use birth control from at least 21 days before randomization through the end of the study

What will I be asked to do?**Screening**

Before you can take part in this experimental study, your health will be checked so we can decide if you qualify to participate. You will need to sign this consent form before screening. If you qualify, then you may take part in the vaccine study.

Screening includes a physical exam and blood tests to check your health, including for HIV. We will ask you about your health history. If you are a female who is able to have children, you will be asked about the possibility of you becoming pregnant while in the study. You will be tested for pregnancy either by collecting your urine or blood. During screening, we will collect some blood to store for research. We will review the test results with you and tell you if the results show that you are eligible to join the study.

Study Procedures

About 30 to 40 people will take part in this study. You will be in the study for about 36 weeks (9 months) and have about 9 clinic visits and 2 telephone contacts. You will get 2 vaccinations, each by injection (shot) in the upper arm muscle. This is called an intramuscular “IM” injection. We will check you for any side effects from

the vaccine.

We will tell you if we learn anything new during this study that might cause you to change your mind about staying in the study. At the end of the study, we will tell you when study results may be available and how to learn about them.

If you agree to take part in the study, you will be randomly assigned (like pulling a number from a hat) to get either:

- The WEVEE vaccine alone (Group 1, Group 3, and Group 5) or,
- The WEVEE vaccine mixed with alum (Group 2, Group 4, and Group 6).

Once enrolled, you will know which group you are in.

The study will start by randomizing people to get a dose of 6 mcg in Group 1 or Group 2. We will review the data after about 2 weeks to make sure this vaccine dose has no safety concerns before we start randomizing people to get the next dose of 30 mcg in Group 3 or Group 4. We will review the data for this dose after about 2 weeks to make sure this vaccine dose has no safety concerns before we start randomizing people to the 60 mcg dose in Group 5 or Group 6.

The table below shows the vaccination plan:

VRC 313				
Group	Subjects	Dose	Day 0	Week 8
1	5	6 mcg	WEVEE	WEVEE
2	5		WEVEE + alum	WEVEE + alum
3	5	30 mcg	WEVEE	WEVEE
4	5		WEVEE + alum	WEVEE + alum
5	5	60 mcg	WEVEE	WEVEE
6	5		WEVEE + alum	WEVEE + alum
Total	30	*Up to 10 more people may be enrolled if needed.		

Each vaccination visit will take about 2 to 3 hours. Other clinic visits will take about 1 to 2 hours. The clinic staff will watch you for at least 30 minutes after each vaccination.

Timepoint	Type of Visit	Duration
Day 0	Enrollment/Vaccination	2 to 3 hours
Day 2	Phone call	15 minutes
Week 2	Follow up clinic visit	1 to 2 hours
Week 4	Follow up clinic visit	1 to 2 hours
Week 8	Second vaccination	2 to 3 hours
Week 9	Phone call	15 minutes
Week 10	Follow up clinic visit	1 to 2 hours
Week 12	Follow up clinic visit	1 to 2 hours
Week 24	Follow up clinic visit	1 to 2 hours
Week 36	Follow up clinic visit	1 to 2 hours

If you are a woman who is able to get pregnant, we will do a pregnancy test before each injection. The test must show that you are not pregnant to get the injection. We may collect urine from you to perform this test.

You will have a telephone call about 2 days after each vaccination so we can check on you.

You will need to complete a diary card at home for 7 days after each vaccination. The purpose of the diary card is so you can write down any symptoms that the vaccine may cause. We will ask you to record your temperature daily and look at the injection site on your arm each day. We will give you a thermometer to measure your temperature and a ruler to measure any skin changes at the injection site. You will get a password to a secure website to enter this data online. If you do not have access to the internet, you may use a paper diary card instead.

If you have any side effects, you should tell a clinic nurse or doctor as soon as possible. You can reach the staff by phone 24 hours a day. If you have symptoms, you may be asked to come to the clinic for an examination before your next scheduled visit. With your consent, we may take a photograph of any reactions you have to the vaccine. It is very important that you follow the instructions from the clinic staff.

At each visit, we will check you for any health changes or problems. We will ask you how you are feeling and if you have taken any new medications. We will draw your blood at each visit, taking up to 5 tubes of blood. We will tell you right away if any of your test results show a health problem. Some blood samples will be used for research only, to study your immune response to the vaccine. Results of these research tests are not used to check your health and will not be given to you.

Who owns my study information and samples?

If you join this study, you will be donating your samples and study information. You will not receive any compensation if your samples or information are used to make a new product. If you withdraw from the study, data and samples that were already collected may be still be used for this study.

Stored Samples

Some of the blood we draw from you during the study will be used by investigators to study proteins and other molecules that may be involved in the immune response. Blood samples will be stored for future research to learn more about WEVEE, vaccines, the immune system, and/or other medical conditions.

The results from the research done with your stored samples are not meant to be used for medical care. They will not be given to your health care provider and will not be put in your medical record.

You may not take part in this study if you are not willing to have your blood samples stored for future analysis.

Labeling of Stored Samples: Your stored samples will be labeled by a special code or number and not your personal information. Only the study team can link this code to you. Any identifying information about you (like name or date of birth) will be kept as confidential as allowable by law.

Risks from Stored Samples: There is a risk of unplanned release of information from your medical records. The chance that this information will be given to an unauthorized person without your permission is very small. Possible problems with the unplanned release of information include discrimination when applying for insurance or employment. Similar problems may occur if you give information yourself or agree to have your medical records released.

Future Studies: In the future, other investigators at NIH or outside of NIH may wish to study your stored samples. When the study team shares your stored samples, they will be marked with a code, but will not have any identifying information on them. Some information about you, like your gender, age, health history, or ethnicity may also be shared with other researchers. Any future research studies using your samples will be conducted in a way that protects the rights and privacy of study participants.

Your stored samples will be used only for research and will not be sold. The research done with your samples may be used to make new products in the future, but you will not get payment for such products.

Making your Choice: You cannot take part in this study if you do not want us to collect or store your blood samples. If you agree to take part in this study, you must also agree to let us keep any of your samples for future research.

What are the possible risks and discomforts?

Possible risks of injections: Temporary stinging, pain, redness, soreness, itchiness, swelling, bruising, or a cut in the arm. There is a very small chance of infection.

Possible risks of any vaccine: Fever, chills, rash, aches and pains, nausea, headache, dizziness, and feeling tired and/or unwell. These reactions are usually greatest within the first 24 hours after vaccination and typically last 1 to 3 days. Over-the-counter medicine, like acetaminophen (Tylenol) or ibuprofen, may be used to help relieve these symptoms.

Very rarely, a serious allergic reaction may occur shortly after any vaccination. This is called “anaphylaxis” and may be life-threatening. While you are waiting in the clinic after the vaccination, we will watch you for anaphylaxis. Treatment for anaphylaxis will be given right away if it occurs.

Possible risks of blood drawing: Pain, bleeding, bruising, feeling lightheaded, fainting, or rarely, infection at the site where the blood is taken.

Possible risks of WEVEE Vaccine: The WEVEE vaccine has not been given to people before and it may have unknown risks or side effects. It has been tested in mice and monkeys. The vaccine did not have any severe side effects and met the safety criteria to be tested in humans. In a study of a similar product, a chikungunya virus VLP vaccine was well tolerated with no reported joint pain or fever after vaccination. No serious adverse events were reported.

Possible risk of aluminum hydroxide suspension: Aluminum adjuvants have been found to be safe for over 60 years. Aluminum-containing vaccines have been associated with reactions of the skin (erythema), bumps in the skin (subcutaneous nodules), contact hypersensitivity and small nodular skin lesions.

Possible risks during pregnancy: We do not know the possible effects of the study vaccines on a fetus or nursing infant. Women who are able to become pregnant must have a negative pregnancy test before each study injection and agree to practice adequate birth control beginning at least 21 days before getting the first injection until the last study visit. If you are pregnant, breast-feeding or want to become pregnant during the next 36 weeks, you cannot take part.

You must also tell the clinic if you think that you are or might be pregnant during this study. If you become pregnant, you will not get any more injections. However, you will be asked to continue with follow-up visits so we can check your health. You will also be asked about the outcome of your pregnancy.

Possible other risks: The safety of the vaccine tested in this study is unknown. It is unknown if the study injection will affect how you respond to any future infection with WEVEE or to any other WEVEE vaccines that you may get in the future. You may not donate blood at a blood bank while taking part in this study. You may not donate blood for one year after your last study injection.

It is possible that the researchers will learn something new during the study about the risks of being in it. If this happens, they will tell you about it. Then you can decide if you want to continue to be in this study or not. You may be asked to sign a new consent form that includes the new information if you decide to stay in the study.

Will I benefit directly from the study?

This study is not designed to benefit you or protect you from infection from these viruses. Others may benefit in the future from the information that will be learned from the study.

Will I be compensated for my time and effort?

You will be compensated for your time and inconvenience as follows for study visits: Screening Visit (1 visit): \$40; Vaccination Visits (2 visits): \$80 each; Follow Up Visits (6 visits): \$60 each.

We may ask you to do extra visits to repeat lab tests or to further assess a safety concern. In those cases, you will receive \$20 compensation for your time and inconvenience. If you do not finish the study, we will compensate you for the visits you have completed. You will get \$560 total, if you complete all scheduled study visits.

Compensation will be provided on a web based, reloadable, debit card (ClinCard) that automates reimbursements. The ClinCard will be provided by study staff at the initial visit (screening).

All payments are made using a personal payment card. We issue this to you for free. The payment card is a prepaid debit card. It can be used exactly like a MasterCard. We load money onto your card electronically every time you need to be paid. The card scheme is run by Greenphire, an independent company specializing in payments for research studies and clinical trials. To issue your card, we need to give Greenphire some of your personal information. Banks and other financial institutions can access this information if they need to verify your identity when you use your card.

Emory University is required by law to report any payments we make to the IRS. To do this, Emory University Department of Finance needs to keep your Social Security Number on file. We are asking you to allow us to communicate your name, address, date of birth, research study name and Social Security Number to Greenphire and Emory University Department of Finance. If you want to receive e-mail or text alerts when payments are made to you, we will ask you to provide your e-mail or phone number as well. All of this information will be stored on computers owned by Greenphire. Greenphire will not have access to any other information collected during this study. Full instructions about using your card are included when we issue it. Please ask if you have any questions or concerns about the card scheme.

We would also like the option of compensating you in the form of cash, check or gift card if ClinCard accessibility is not available. You will be asked to fill out a tax form, including your Social Security or Taxpayer Identification Number, in order to be reimbursed, depending on the amount and method of payment. Some payment methods involve mail coming to your house, which may be seen by others in your household. You can decline payment if you are concerned about confidentiality, or you can talk to the study team to see if there are other payment options. You will need to fill out a W-9 form.

What are my other options?

This study is not designed to treat or prevent any disease. You may choose not to take part in this study. You may be eligible for other studies.

How will you protect my private information that you collect in this study?

Whenever possible, a study number, rather than your name, will be used on study records. Your name and other identifying information will not appear when we present or publish the study results.

Certain offices and people other than the researchers may look at study records. Government agencies and Emory employees overseeing proper study conduct may look at your study records. These offices include The Food and Drug Administration, the Office for Human Research Protections, the sponsor, the Emory Institutional Review Board, the Emory Office of Research Compliance. Study funders may also look at your study records. Emory will keep any research records we create private to the extent we are required to do so by law. A study number rather than your name will be used on study records wherever possible.

Certificate of Confidentiality

There is a Certificate of Confidentiality from the National Institutes of Health for this Study. The Certificate of Confidentiality helps us to keep others from learning that you participated in this study. Emory will rely on the Certificate of Confidentiality to refuse to give out study information that identifies you. For example, if Emory received a subpoena for study records, it would not give out information that identifies you.

The Certificate of Confidentiality does not stop you or someone else, like a member of your family, from giving out information about your participation in this study. For example, if you let your insurance company know that you are in this study, and you agree to give the insurance company research information, then the investigator cannot use the Certificate to withhold this information. This means you and your family also need to protect your own privacy.

The Certificate does not stop Emory from making the following disclosures about you:

- Giving state public health officials information about certain infectious diseases.
- Giving law officials information about abuse of a child, elderly person or disabled person.
- Giving out information to prevent harm to you or others.
- Giving the study sponsor or funders information about the study, including information for an audit or evaluation.

Storing and Sharing your Information

To advance science, it is helpful for researchers to share information they get from studying humans by putting it into shared scientific databases. Researchers can then study the information combined from many studies to learn even more about health and diseases.

If you agree to take part in this study, some of your data will be placed into one or more scientific databases. We will remove identifying information like your name, address, and birth date. The data may then be used for future research and shared broadly for research purposes. Only researchers who are approved to access the database may be able to see and use your information. You will not get any direct benefits from future research that uses your data and information.

In general, we will not give you any individual results from the study of the samples you give us. If we find something of urgent medical importance to you, we will inform you, although we expect that this will be a very rare occurrence.

Genetic Testing

Some genetic tests are done in research studies to see if genetic differences in people cause different types of immune responses. Genetic testing will not be done in this study, but may be performed on stored samples at later time. If genetic tests are done at a later time, your name and identifying information will not be on your samples and the results will not be in your medical record. These tests are not used to check your health and we will not tell you the results.

How is my Genetic Information Protected? What are the Risks?

The Genetic Information Nondiscrimination Act (GINA) is a federal law that generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Be aware that GINA does **not** protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance, and does not apply to employers with less than 15 employees.

In addition to GINA, the State of Georgia has laws that prohibit insurers from using genetic testing information for any non-treatment purpose. However, like GINA, this state law protection has exclusions: life insurance policies, disability income policies, accidental death or dismemberment policies, Medicare supplement policies, long-term care insurance policies, credit insurance policies, specified disease policies, hospital indemnity policies, blanket accident and sickness policies, franchise policies issued on an insurance policy written as a part of workers' compensation equivalent coverage, or other similar limited accident and sickness policies.

Privilege

In the State of Georgia, in some circumstances your genetic information may have special legal protections called "privilege." This means that the information cannot be used as evidence in a court. By allowing us to use and disclose your genetic information for this research study along with other information about you that genetic information used in the research may no longer have that legal protection. Other protections described in this form will still apply. There are also other confidentiality protections for research data in general under Georgia state law.

Who will monitor the study?

This study will be monitored by a group of physicians and scientists associated with the NIH. This group will review the study information and will pay close attention to any reactions. If there are serious side effects, study injections may be delayed or canceled.

Your research study charts may be reviewed by the IND Sponsor representatives.

Conflict of Interest

The NIH developed the investigational product being used in this research study. The results of this study could play a role in whether the FDA will approve the study product for sale at some time in the future. If approved, the future sale of the study product could lead to payments to NIH and some NIH scientists. By U.S. law, government scientists are required to get such payments for their inventions. You will not get any money from the development or sale of the product.

Medical Record

If you have been an Emory Healthcare patient before, then you already have an Emory Healthcare medical record. If you have never been an Emory Healthcare patient, you do not have one. An Emory Healthcare medical record will be made for you if an Emory provider or facility gives you any services or procedures for this study.

We will take reasonable steps to keep copies of this form out of Emory Healthcare's medical records system. If we aren't successful in keeping these forms out, despite our efforts, we will take steps to remove them. If they cannot be removed, we will take steps to limit access to them.

Emory Healthcare may create study information about you that can help with your care. For example, the results of study tests or procedures. These study results will be put in your Emory Healthcare medical record. Anyone who has access to your medical records will be able to have access to all the study information placed there. The confidentiality of the study information in your medical record will be protected by laws like the HIPAA privacy rule. State and federal laws may not protect the research information from disclosure. We will ask for your authorization if we need to obtain any information from your medical record.

We will also keep a separate research record of all study tests and procedures that we will use for research purposes. For this study, those items include: safety laboratory tests and pregnancy tests. This research record will not be a part of your medical record.

Tests and procedures done at non-Emory places may not become part of your Emory medical record. Also, if you decide to be in this study, it is up to you to let your other health providers know.

In Case of Injury

If you believe you have become ill or injured from this research, you should contact Dr. Edupuganti at telephone number [REDACTED]. You should also let any health care provider who treats you know that you are in a research study.

If you get ill or injured from being in the study, Emory will help you to get medical treatment. We will provide emergency treatment for any immediate reactions to the study products at the Hope Clinic. Neither Emory nor the sponsor will pay for your medical treatment you may receive outside of the Hope Clinic. Your insurer will be billed for your treatment costs. If you do not have insurance, or if your insurance does not pay, then you will have to pay these costs.

Emory and the sponsor have not, however, set aside any money to pay you if you are injured as a result of being in this study or to pay for this medical treatment. For Emory, the only exception is if it is proven that your injury or illness is directly caused by the negligence of an Emory employee. "Negligence" is the failure to follow a standard duty of care. You do not give up any legal rights you may have by being in this study, including any right to bring a claim for negligence.

Costs

There will be no costs to you for participating in this study, other than basic expenses like transportation. You will not be charged for any of the research activities. If the study procedures result in any medical complications that would not fall under "injury" as discussed above, the cost of treatment for those complications may be charged to you or your insurance.

Withdrawal from the Study

Your participation in this study is completely voluntary. You can choose to stop taking part in the study at any time. There is no penalty or loss of benefits for choosing to leave the study.

If you get the first injection but not the second, we still want you to continue with all planned follow-up visits until the end of the study. It is important that we continue to check your health even if you do not get the second vaccination.

The researchers also have the right to stop your participation in this study without your consent for any reason, especially if they believe it is in your best interest or if you were to object to any future changes that may be made in the study plan.

These are the expected reasons why the researchers may stop your participation:

- You do not keep appointments or follow study procedures.
- You get a serious illness that needs ongoing medical care.
- You need to get treatment with a medication that affects your immune system (such as a steroid like prednisone).
- You enroll in another research study at the same time you are in this study.
- You become pregnant.
- The study is stopped by regulatory agencies, the study sponsor or study investigators. If this happens, we will tell you why.

Contact Information

Contact Dr. Sri Edupuganti at [REDACTED]:

- if you have any questions about this study or your part in it,
- if you feel you have had a research-related injury or a bad reaction to the study vaccine, or
- if you have questions, concerns or complaints about the research

Contact the Emory Institutional Review Board [REDACTED]:

- if you have questions about your rights as a research participant.
- if you have questions, concerns or complaints about the research.
- You may also let the IRB know about your experience as a research participant through our Research Participant Survey at [REDACTED]

Consent

If you decide to participate in this study, your samples will be stored for future use. This is a requirement for participation in the study. However, the study team wants to make sure that you are aware of this and that you agree to have your samples stored. Please initial one of the options below to indicate your choice:

_____ Yes, I agree to let the sponsor store my samples.
(Initial)

_____ No, I do not agree to let the sponsor store my samples.
(Initial)

TO BE FILLED OUT BY SUBJECT ONLY

Please **print** your name, **sign**, and **date** below if you agree to be in this research study. By signing this consent and authorization form, you will not give up any of your legal rights. We will give you a copy of the signed form to keep.

Name of Subject

_____ : _____ am / pm
Signature of Subject (18 or older and able to consent) **Date** **Time**

TO BE FILLED OUT BY STUDY TEAM ONLY

Name of Person Conducting Informed Consent Discussion

_____ : _____ am / pm
Signature of Person Conducting Informed Consent Discussion **Date** **Time**