Protocol Title: VRC 614 (000536): A Phase 1, Dose Escalation, Open-Label Clinical Trial with Experimental Controlled Human Malaria Infections (CHMI) to Evaluate Safety and Protective Efficacy of an Anti-Malaria Human Monoclonal Antibody, VRC-MALMAB0114- 00-AB (L9LS), in Healthy, Malaria-Naive Adults

NCT: 05019729

Documents:

- IRB-approved Protocol (v2.0 03NOV2021) - Statistical Analysis Considerations located in Section 6 of the Protocol
- IRB approved ICF (v2.0 03NOV2021) - IRB Approval/Document Date: 01DEC2021

Version 2.0
November 3, 2021

VACCINE RESEARCH CENTER

Protocol VRC 614
NIH 000536

Title: A Phase 1, Dose Escalation, Open-Label Clinical Trial with Experimental Controlled Human Malaria Infections (CHMI) to Evaluate Safety and Protective Efficacy of an Anti-Malaria Human Monoclonal Antibody, VRC-MALMAB0114-00-AB (L9LS), in Healthy, Malaria-Naive Adults

Abbreviated Title: L9LS in Healthy Adults

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

IND 155252

Investigational Product L9LS Manufacturer:
Vaccine Clinical Materials Program (VCMP) operated under contract
by Leidos Biomedical Research, Inc.,
Frederick, Maryland, US

NIH Principal Investigator: Richard Wu, M.D.
VRC/NIAID
[redacted]
Email: richard.wu2@nih.gov

TABLE OF CONTENTS

LIST OF TABLES

ABBREVIATIONS

Abbreviation	Definition
ADA	Anti-Drug Antibody
AE	Adverse event
ALT	Alanine aminotransferase
ANA	Anti-nuclear antibody
AST	Aspartate aminotransferase
CBC	Complete blood count
cGLP	Current Good Laboratory Practices
cGMP	Current Good Manufacturing Practices
CHI	Controlled human infection
CHMI	Controlled human malaria infection
CMP	Comprehensive Metabolic Panel
CRF	Case Report Form
CRO	Contract Research Organization
CSP	Circumsporozoite protein
CTP	Clinical Trials Program
DoD	Department of Defense
DoDI	Department of Defense Instruction
DNA	Deoxyribonucleic Acid
DOT	Directly observed therapy
EKG	Electrocardiogram
ELISA	Enzyme-linked immunosorbent assay
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
HRPP	Human Research Protections Program
HSBP	Human Subjects Protection Branch
ICH	International Conference on Harmonization
IM	Intramuscular
IND	Investigational New Drug Application
IV	Intravenous
LIMS	Laboratory Management Information System
mAb	Monoclonal Antibody
MedDRA	Medical dictionary for regulatory activities
MO	Medical Officer
NAT	Nucleic acid test
NHP	Non-Human Primate
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NIH CC	NIH Clinical Center

Abbreviation	Definition
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase Chain Reaction
Pf	*Plasmodium falciparum*
PfCSP	*Plasmodium falciparum* circumsporozoite protein
PfSPZ	*Plasmodium falciparum* whole-sporozoite
PI	Principal Investigator
PK	Pharmacokinetics
PSRT	Protocol Safety Review Team
QA	Quality Assurance
RBC	Red blood cells
rPfCSP	Recombinant *Plasmodium falciparum* circumsporozoite protein
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SC	Subcutaneous
SPZ	Sporozoite
SUSAR	Serious and unexpected suspected adverse reaction
TCR	Tissue Cross Reactivity
U.S.	United States
ULN	Upper limit of normal
UPnonAE	Unexpected Problem that is not an Adverse Event
VCMP	Vaccine Clinical Materials Program
VEC	Vaccine Evaluation Clinic
VIS	Volunteer Infection Studies
VIP	Vaccine Immunology Program
VRC	Vaccine Research Center
WBC	White blood cells
WHO	World Health Organization
WRAIR	Walter Reed Army Institute of Research

PRINCIPAL INVESTIGATOR PROTOCOL SIGNATURE PAGE

VRC 614: A Phase 1, Dose Escalation, Open-Label Clinical Trial with Experimental Controlled Human Malaria Infections (CHMI) to Evaluate Safety and Protective Efficacy of an Anti-Malaria Human Monoclonal Antibody, VRC-MALMAB0114-00-AB (L9LS), in Healthy, Malaria-Naive Adults

I, the Principal Investigator for the study site indicated below, agree to conduct the study in full accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct the study in compliance with United States (US) Health and Human Services (HHS) regulations (45CFR 46); applicable US Food and Drug Administration (FDA) regulations; standards of the International Conference on Harmonization Guidelines for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee (IRB/EC) determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health) and institutional policies. 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. The protocol signature page will be signed for subsequent protocol approvals.

I agree to maintain all study documentation pertaining to the conduct of this study, including but not limited to, case report forms, source documents, laboratory test results, and medication inventory records, per FDA regulation (21 CFR 312.62) and all applicable requirements. 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 for review prior to submission.

I have read and understand the information in this protocol 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.

Richard Wu/Clinical Fellow	NIH - Vaccine Evaluation Clinic
Name/Title of Principal Investigator	Study Site Name
Signature of Principal Investigator	Date

PRÈCIS

Title: **VRC 614**: A Phase 1, Dose Escalation, Open-Label Clinical Trial with Experimental Controlled Human Malaria Infections (CHMI) to Evaluate the Safety and Protective Efficacy of an Anti-Malaria Human Monoclonal Antibody, VRC-MALMAB0114-00-AB (L9LS), in Healthy, Malaria-Naïve Adults.

Design: This is the first in human study of the VRC-MALMAB0114-00-AB (L9LS) monoclonal antibody (mAb) targeting the *Plasmodium falciparum* (Pf) circumsporozoite protein (PfCSP) in healthy adults. This dose-escalation study will evaluate the safety, tolerability, pharmacokinetics (PK), and protective efficacy of L9LS. The primary hypothesis is that L9LS will be safe and well tolerated when administered by intravenous (IV), subcutaneous (SC) or intramuscular (IM) routes. The secondary hypotheses are that L9LS will be detectable in human sera with a definable half-life and confer protection following a controlled human malaria infection (CHMI).

Study Product: VRC-MALMAB0114-00-AB was isolated and developed by the Vaccine Research Center (VRC), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH) and binds an epitope of the PfCSP.

Subjects: Healthy adults, 18-50 years of age, who are malaria-naive.

Study Plan: This study will evaluate the L9LS doses and routes of administration as shown below in the Study Schema table. The study will start with enrollment into Group 1. Assessment of safety will include solicited reactogenicity, clinical observation and monitoring of hematological and chemical parameters at clinical visits throughout the study. Interim safety evaluations will occur and must support continued evaluation of L9LS prior to enrolling subjects into additional dose groups. L9LS recipients in Groups 1-4 will participate in the CHMI. Group 5 will not receive investigational product in order to serve as the control group for the CHMI. After CHMI, all participants will be evaluated for malaria parasitemia. Subjects who develop blood stage infection will be treated as soon as identified per protocol criteria. Subjects in Group 6 will receive investigational product but will not take part in the CHMI. Blood sampling for PK analysis will occur throughout the study, including pre- and post-CHMI.

VRC 614 Study Schema

Group	Subjects	L9LS Administration		CHMI
		Dose (mg/kg)	Route	
1	5	1	IV	X
2	4	5	IV	X
3	5	5	SC	X
4	4	20	IV	X
5	6	Control[1]		X
6	5	5	IM	N/A
Total	29[2]	[1]Two (2) additional control subjects will be enrolled as CHMI back-ups [2]Up to 40 subjects may enroll if needed for additional safety or efficacy evaluations.		

Duration: Study follow-up will continue through 24 weeks post product administration or 8 weeks post CHMI, whichever is most stringent.

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1. INTRODUCTION

Malaria is a mosquito-borne protozoan disease belonging to the genus Plasmodium that affects 250-500 million people, and kills approximately 500,000 individuals annually, with an enormous economic impact in the developing world, especially sub-Saharan Africa [1-3]. The five recognized species of Plasmodium that cause human malaria infection are *Plasmodium falciparum* (Pf), *P. vivax, P. ovale, P. malariae,* and *P. knowlesi*. Among these, Pf causes more deaths in children worldwide than any other single infectious agent. An estimated 30,000 travelers from North America, Europe, and Japan contract malaria per year. Although malaria is preventable with chemoprophylaxis and completely curable with early intervention, drug treatment is not readily accessible in many parts of the world. Additionally, the use of antimalarial drugs over time has been associated with the emergence of drug-resistant strains. Lack of compliance with preventive drug treatment by individuals travelling to endemic areas may also result in fatal malaria infection. The world's first malaria vaccine, RTS,S/AS01 (Mosquirix™), a recombinant protein-based vaccine targeting Pf, was approved for use by European regulatory authorities in 2015. It is currently being evaluated in immunization programs in sub-Saharan Africa despite having been found to provide only partial protection (of about 30-50%) against clinical malaria to children and infants [4, 5]. Therefore, the development of a safe and more effective malaria vaccine is an urgent priority and may take many additional years. Alternatively, the use of antibodies for passive prevention of malaria provides a new and more immediate approach for malaria prevention that, if successful, would have a major impact on improving public health worldwide. Recent development of highly potent human monoclonal antibodies that have changes made to improve their duration *in vivo* and protect in different pre-clinical models will provide the first assessment of this approach.

1.1. Study Rationale

1.1.1. L9LS Development

The Vaccine Research Center (VRC), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH) has been investigating broadly-neutralizing human monoclonal antibodies (bNAbs) targeted at a variety of pathogens that may be utilized in clinical applications including preventive and therapeutic measures. In the case of malaria, prevention by passive immunization has potential applications for use in travelers, military personnel, season control and elimination campaigns in endemic areas.

L9LS (VRC-MALMAB0114-00-AB) is the second PfCSP-specific mAb the VRC plans to pursue in clinical development. L9, the wild-type parent of L9LS, was isolated by sorting the PfCSP-reactive memory B cells obtained from a subject immunized with a radiation-attenuated PfSPZ malaria vaccine in the VRC 314 clinical trial (NCT02015091) using a junctional epitope mimic probe designed to select for "CIS43-like" mAbs. Epitope mapping showed L9 bound to NPNV motifs associated with NVDP minor repeats of PfCSP. When compared to a published panel of protective human PfCSP mAbs, L9 protected mice against intravenous and mosquito bite SPZ challenge, and demonstrated the lowest effective dose (ED)80 and effective concentration (EC)80 values (325.7 µg and 145.1 µg/mL, respectively) of any mAb evaluated, including CIS43LS (685.92 µg and 363.93 µg/mL, respectively) [6]. The unique preference of L9 for NPNV motifs was further underscored by the fact that all four NVDP tetrapeptide motifs had to be mutated to NANP to disrupt the recognition of L9 for the NPNV motifs found in

rPfCSP. As 100% of known *Pf* field isolates have one or more NVDP motifs, these data suggest that L9 should bind all circulating strains of malaria[6].

L9 was modified with the previously-described Fc-region LS mutation (L9LS) to increase neonatal Fc receptor (FcRn) binding and consequent antibody half-life [2-5]. Immune protection and half-life data acquired with L9 and L9LS identify L9LS as a promising clinical candidate for passive malaria prophylaxis.

1.1.2. Rationale for Study Design

This phase I trial will evaluate L9LS safety and PK at doses 1, 5 and 20 mg/kg IV, 5 mg/kg SC, and 5 mg/kg IM. The study will allow for the achievement of a range of antibody concentrations in vivo for determining a protective L9LS titer in CHMI. Because the safety and potential therapeutic range of this mAb is unknown, dose selection was informed by non- clinical PK data in non-human primates (NHP) comparing L9 and L9LS, historical dose ranges evaluated in clinical trials of other mAbs developed by the VRC (e.g., VRC07-523LS [IND133027] and N6LS [IND 134081]), and prior clinical experience in healthy adults with anti-malaria mAb CIS43LS (VRC 612 [NCT04206332] conducted under IND 142632 [7]) where recipients were protected against malaria infection when challenged in CHMI at about 4 weeks to 36 weeks post-product administration. The lack of malaria infection in participants who received a 20 or 40 mg/kg IV dose of CIS43LS prevented the planned regression analysis to identify a threshold level of protection. The higher participant numbers in the 1 mg/kg IV and 5 mg/kg SC groups allow for more data at the lowest dose group to try to identify a protective antibody titer threshold and to support future trials assessing the SC route in malarial-endemic regions, respectively.

1.1.3. Addition of Intramuscular Injection Cohort in v.2.0

With the version 2.0 amendment, a cohort is being added to receive a 5 mg/kg dose of L9LS by IM injection. The purpose of this amendment is to evaluate the safety, tolerability and PK of L9LS by the IM route. Data on this route may support development of phase 2 trials in Africa as the IM route may allow individuals, such as children, who may not have sufficient subcutaneous tissue or not have intravenous access, to be able to receive L9LS. Since this arm is being added after the CHMI has occurred, this group will not participate in the CHMI.

1.2. Background

1.2.1. Previous Human Experience

There is no human experience with L9LS prior to this trial. Prior clinical experience in completed and ongoing Phase 1 and 2 trials of healthy adults with human mAbs manufactured and formulated by the VRC that recognize pathogen-specific epitopes (i.e., VRC01, VRC01LS, VRC07-523LS, and mAb114) [8-11] are used to summarize the general safety risk associated with mAbs.

Treatments with these mAbs have been generally well tolerated, with no reported deaths or serious adverse events (SAEs) assessed as related to the study products. Typical for mAbs, the predominant local reactogenicity complaint has been mild pain/tenderness, although reports of mild injection site pruritus, redness and swelling have occurred at modestly higher frequencies

with SC administration. Malaise, muscle pain, and headache have been the most frequently reported solicited complaints noted in the 3 days post product administration and these have also been mostly transient and mild in severity. Increased frequencies of fever, redness, swelling and pain at the injection site have been reported after IM administration. Urticaria and infusion reactions comprised of chills, rigors, myalgia, headache, and/or fever have been reported after IV infusions at product doses of 10 to 40 mg/kg; these reactions have been transient, resolved without sequelae within 24 hours of onset, and treated with over-the-counter analgesics and antipyretics.

1.2.2. Controlled Human Infections (CHI)

Controlled human infection (CHI) trials (also referred to as Volunteer Infection Studies (VIS)) result in the experimental infection of healthy subjects with the infectious agent of choice and are an unparalleled tool in infectious disease research. CHI trials allow for the accelerated evaluation of novel drugs and vaccines for potential efficacy, while also providing the opportunity to prospectively study clinical disease progression. The first controlled human malaria infection (CHMI) was performed in the mid-1980s [12]. This process involves the deliberate infection with malaria parasites either by mosquito bite or direct injection. VRC has successfully conducted three Phase 1 CHMI studies: VRC 312 [13], VRC 314 [14], and VRC 612 [7].

According to a comprehensive review of CHI trials using a variety of pathogens, an estimated 6000 subjects have received CHI [15]. Only four possibly-related SAEs have been reported, of which two were observed following malaria vaccination and CHMI [15]. The first cardiac event of possible myocarditis, reported in 2008 [16], prompted recommendation by a panel of experts that consideration of cardiac risk be required for clinical challenge trials and that individuals identified as at increased cardiovascular risk be excluded from malaria clinical challenge trials [17]. A second cardiac event was observed in 2013 following malaria vaccination and CHMI [18]. VRC was also informed of a possible 3rd, unpublished, myocarditis event in 2014. As a result of these events and the recommendations, evidence of increased cardiovascular disease risk or an electrocardiogram (ECG) with clinically significant abnormalities will preclude trial enrollment as described in Section 4.1.2.

The challenge phase in this study will be performed with Pf strain 3D7 [sensitive to Chloroquine and Malarone (atovaquone and proguanil)] via mosquito bite, which is the natural route of exposure and transmission in the field. While subjects will be monitored closely throughout study duration, monitoring intensity will increase following exposure to Pf-infected mosquitoes to ensure rapid diagnosis and treatment. Appropriate drug therapy will be used to treat and cure any subject with a confirmed Pf infection after diagnosis by PCR, the most sensitive assessment for detecting early malaria infection, in order to minimize the risk of developing a serious complication. The Pf strain to be used for CHMI in this study can be effectively treated with and cured by the antimalarial medications to be used in this trial [19, 20].

There is negligible risk of transmitting malaria to a person in the community since subjects are exposed to malaria-infected mosquitos only during the CHMI at a contained facility.

1.3. Laboratory Assessments of L9LS

Some laboratory assessments in this study are also designed to characterize the investigational product. This includes PK analysis and evaluation for anti-drug antibody (ADA) development after product exposure. These are further described in the subsequent sections. Other assays may also be performed using stored samples at a later date if additional assessments are needed.

The VRC's Vaccine Immunology Program (VIP), Gaithersburg, MD, will process blood and store coded samples, and will either perform sample testing or ship coded samples to designated research laboratories at the VRC or other approved collaborators. See APPENDIX I for schedules, blood volumes and tube types to be used for research sample collection. Research assays will be performed on samples from both study product recipients and CHMI-controls at baseline and throughout the study.

Tube types for clinical labs are according to institutional requirements and are shown in the Schedule of Evaluations to estimate blood volumes. Different tubes for clinical evaluations may be used to meet site requirements. Research sample tube types and blood volumes must be used as shown or as otherwise instructed by the IND Sponsor. In some instances, coded samples may be transported directly by study staff to the laboratory of an approved collaborator.

1.3.1. Pharmacokinetic (PK) Analysis

Concentrations of L9LS will be measured by Meso Scale Discovery (MSD) platform and similar methodology as previously described for other VRC mAb products [9].

1.3.2. Detection of Anti-Drug Antibody

Assays for detection of ADA will be performed at specified timepoints following product administration and CHMI compared to baseline status using a similar methodology as previously described for other VRC mAb products [9]. We will employ a sequential approach to screen, confirm, and characterize ADA in the clinical serum samples according to the Food and Drug Administration (FDA) guidance. Screening and confirmation will involve an MSD electrochemiluminescence (ECL) bridging assay.

1.4. Measures of mAb-Mediated Protection and Parasitemia

L9LS-mediated protection will be assessed after CHMI outcomes are obtained and compared to control subjects' CHMI outcomes. The endpoint defining mAb-mediated protection for the CHMI is the absence of Pf parasites in blood samples obtained from L9LS-recipients collected daily from Day 7 through Day 17 and then on Day 21 post-CHMI. The criteria for a case of malaria is confirmation of parasitemia either by the Malaria real-time PCR assay or by blood smear. The Malaria real-time PCR assay targets the 18S rRNA (ribosomal RNA) gene, which is a DNA target. It is the default means of monitoring for parasitemia in this protocol; a single positive PCR result will confirm infection [13, 21, 22].

A blood smear will be performed by the NIH Clinical Center Microbiology Service per their departmental SOPs for any subject who develops symptoms likely due to malaria despite having a negative PCR result. Laboratory personnel performing PCR and blood smear testing will be blinded to subject group and treatment received or lack thereof, in the case of controls. Research blood samples may also be used for parasite genome analysis.

2. STUDY PRODUCT AND CHMI

2.1. Study Product: L9LS

The L9LS (VRC-MALMAB0114-00-AB) mAb was discovered and developed by the VRC, NIAID, NIH. The study product was manufactured under current Good Manufacturing Practice (cGMP) by the Vaccine Clinical Materials Program (VCMP) operated under contract by Leidos Biomedical Research, Inc., Frederick, MD.

2.2. Preclinical Experience

To assess L9LS as a candidate for clinical trials, research grade mAb was assessed for *in vitro* functional activity including binding properties and auto-reactivity, *in vivo* protection following challenge using a mouse infection model, and *in vivo* PK using an NHP model. In mice, L9 was more potent than CIS43, and both L9LS and L9 mediated the same potency following challenge. In NHP PK studies, L9LS exhibited substantially longer half-life in blood as compared to the parental L9 mAb without the LS mutation.

Two preclinical toxicology studies were conducted with a process-representative developmental batch of L9LS. An *in vitro* tissue cross-reactivity (TCR) assay to screen for potential cross-reactivity and an *in vivo* rat toxicity study to demonstrate safety were both conducted in compliance with Title 21 of the Code of Federal Regulations Part 58 (21 CFR 58) Good Laboratory Practice (GLP) for Nonclinical Laboratory Studies.

2.2.1 Tissue Cross-Reactivity (TCR) Study

The TCR assay screened a standard panel of normal human tissues (three donors per tissue) and Sprague Dawley rat tissues (two rats per tissue). Mammalian cells transfected to express CSP were used as a tissue positive control. Two concentrations of L9LS were tested: 1.15 µg/ml (selected as the concentration which saturated the positive control tissue), and 11.5 µg/ml (10-fold excess). A negative control IgG1κ antibody (GR338422-1, no mammalian target antigen) was tested at the same two concentrations. L9LS exhibited scattered specific membrane binding in 3/3 human salivary gland tissue samples, which localized to the epithelial cells lining the ducts and acini. Binding was rare (1-5% of these epithelial cells) at 1.15 µg/ml, and rare to occasional (5-25% of these epithelial cells) at 11.5 µg/ml. The cause of the salivary epithelial cell membrane binding has not been identified. Specific membrane binding to salivary gland tissue was not observed for the negative control antibody. L9LS did not bind to rat salivary epithelium. No specific membrane-binding to other human tissues was observed.

2.2.2 Rat Toxicity Study

Sprague Dawley rats were dosed with L9LS to evaluate toxicity and toxicokinetics. Rats received 0, 40, or 400 mg/kg by intravenous (IV) bolus injection twice (Day 1 and Day 11). Female rats were dosed with 10 mg/kg by subcutaneous (SC) injection once (D1); male rats were dosed with 10 mg/kg SC twice (D1 and D11); both male and female rats were dosed with 100 mg/kg SC twice (Day 1 and Day 11). For all dose-levels, the main-group was necropsied at Day 12 to evaluate potential immediate effects, and recovery animals were necropsied at Day 46 to evaluate the potential for delayed effects and recovery. Treated rats exhibited a transient increase in body temperature post-dose (up to + 0.5ºC, considered a non-adverse response).

Serum clinical chemistry tests detected slightly-increased globulin, consistent with the administration of L9LS, an IgG mAb. For IV dosing, the no observed adverse effect level (NOAEL) was the high dose, 400 mg/kg IV x2. For SC dosing, the NOAEL was the high-dose, 100 mg/kg SC x2. SC injection of L9LS did not cause reactogenicity (edema, erythema, eschar) in any rat. Histopathology evaluation of the SC injection site skin reported minimal to moderate subcutaneous mixed cell infiltration, considered treatment-related and predictive for human volunteers. One treated rat (in the 100 mg/kg SC group) was found dead; this event was attributed to a procedural error the previous day and is not considered treatment-related. One treated female (in the 100 mg/kg SC recovery group) had grossly-visible heart enlargement (2-fold increase in both heart weight and heart:body weight compared to the control means), with normal heart histology. Spontaneous cardiomyopathies are occasionally observed for the Sprague Dawley strain of rat. Based on the singular incidence, this observation is not considered treatment-related.

With reference to the CDER 2005 Guidance for Industry Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers[1], scaling based on body weight is appropriate for a mAb expected to distribute mainly in the vascular space. The rat IV NOAEL of 400 mg/kg x2 supports the IV clinical high-dose with a 20-fold dose margin. The rat SC NOAEL of 100 mg/kg x2 supports the SC clinical dose with a 20-fold dose margin.

The FDA provides guidance on "the nonclinical safety studies recommended to support human clinical trials" in the Guidances for Industry ICH M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals[2] and ICH S6 Addendum to Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals[3]. Taken together, the L9LS TCR and rat toxicity study results meet the safety standard set in these guidances and support proceeding with the proposed L9LS clinical trial.

2.3. Clinical Experience

This study constitutes the first in human trial with L9LS, therefore, there is no previous experience in humans. See Section 1.2.1 for more information about similar VRC mAb products. As additional data about the effect of L9LS in humans is accumulated from the cohorts of this first-in-human Phase 1 trial, this section will be updated.

2.4. Controlled Human Malaria Infection (CHMI)

Preparation of infected mosquitoes for CHMI will be performed according to a Type II Master File 033797, Malaria Challenge Model, Standard Operating Procedures for the Pf model used. To prepare infected mosquitoes, Pf asexual and sexual erythrocytic stage parasites will be grown in normal human erythrocytes using standard culture medium containing 10% normal human serum. The blood and serum for culture are purchased from a Food and Drug Administration (FDA)-accredited blood bank. Each shipment carries a certificate of analysis certifying that the blood products are negative or non-reactive for immunologic evaluation and infectious disease testing.

[1] https://www.fda.gov/media/72309/download
[2] https://www.fda.gov/media/71542/download
[3] https://www.fda.gov/media/78034/download

3. STUDY OBJECTIVES

3.1. Primary Objectives

- To evaluate the safety and tolerability of L9LS administered IV at 1, 5, and 20 mg/kg in healthy, malaria-naive adults
- To evaluate the safety and tolerability of L9LS administered SC at 5 mg/kg in healthy, malaria-naive adults
- To evaluate the safety and tolerability of L9LS administered IM at 5 mg/kg in healthy, malaria-naive adults

3.2. Secondary Objectives

- To evaluate the pharmacokinetics of L9LS at each dose level throughout the study
- To determine if IV or SC administration of L9LS mediates protection against infectious *P. falciparum* following CHMI

3.3. Exploratory Objectives

- To determine whether anti-drug antibody (ADA) to L9LS can be detected in sera of recipients at specific time points throughout the study
- To assess for IgG1 allotypes and allotype-specific effects on L9LS pharmacokinetics

4. STUDY DESIGN AND CLINICAL PROCEDURES

This open-label, dose escalation study will be conducted at the VRC Vaccine Evaluation Clinic (VEC) in the NIH Clinical Center (NIH CC) and the CHMI will be conducted at the Walter Reed Army Institute of Research (WRAIR) insectary with the oversight of NIH staff. The primary hypothesis is that L9LS will be safe and tolerable when administered by either IV, SC, or IM routes. The secondary hypotheses are that L9LS will be detectable in human sera with a definable half-life and will confer protection following a CHMI.

This study will evaluate L9LS at the doses and routes as shown below in the Study Schema table. The study will start with enrollment into Group 1. Assessment of safety will include solicited reactogenicity, clinical observation and monitoring of hematological and chemical parameters at clinical visits throughout the study. Interim safety evaluations will occur and must support continued evaluation of L9LS prior to enrolling subjects into additional dose groups. L9LS recipients in Groups 1-4 will participate in the CHMI. Group 5 will not receive investigational product in order to serve as the control group for the CHMI. After CHMI, participants in Groups 1-5 will be evaluated for malaria parasitemia. Subjects who develop blood stage infection will be treated as soon as identified per protocol criteria. Subjects in Group 6 will receive investigational product but will not take part in the CHMI. Blood sampling for PK analysis will occur throughout the study, including pre- and post-CHMI.

Table 1: Study Schema

VRC 614 Study Schema				
Group	**Subjects**	**L9LS Administration**		**CHMI**
		Dose (mg/kg)	**Route**	
1	5	1	IV	X
2	4	5	IV	X
3	5	5	SC	X
4	4	20	IV	X
5	6	Control[1]		X
6	5	5	IM	N/A
Total	29[2]	[1]Two (2) additional control subjects will be enrolled as CHMI back-ups. [2]Up to 40 subjects may enroll if needed for additional safety or efficacy evaluations.		

4.1. Study Population

Subjects will be screened to confirm eligibility requirements for participation using the VRC 500 screening protocol. The screening and education process required prior to enrollment is designed to ensure that subjects comprehend the purpose, details and risks/benefits of the study.

4.1.1. Inclusion Criteria

A subject must meet all of the following criteria to be included:

1. Able and willing to complete the informed consent process
2. Able to provide proof of identity to the satisfaction of the study clinician completing the enrollment process
3. Available for clinical follow-up through the last study visit

4. 18 to 50 years of age
5. In good general health without clinically significant medical history
6. Physical examination without clinically significant findings within the 56 days prior to enrollment
7. Weight ≤ 115 kg (except Group 5)
8. Adequate venous access if assigned to an IV group or adequate subcutaneous tissue if assigned to an SC group
9. Willing to have blood samples collected, stored indefinitely, and used for research purposes
10. Agrees to participate in a controlled human malaria infection (CHMI) and to comply with post-CHMI follow-up requirements (except Group 6)
11. Agrees to refrain from blood donation to blood banks for 3 years following participation in CHMI (except Group 6)
12. Agrees not to travel to a malaria endemic region during the entire course of study participation (except Group 6)

Laboratory Criteria within 56 days prior to enrollment:

13. WBC 2,500-12,000/mm^3
14. WBC differential either within institutional normal range or accompanied by the Principal Investigator (PI) or designee approval
15. Platelets = 125,000 – 500,000/mm^3
16. Hemoglobin within institutional normal range or accompanied by the PI or designee approval
17. Creatinine ≤ 1.1 x upper limit of normal (ULN)
18. Alanine aminotransferase (ALT) ≤1.25 x ULN
19. Negative for HIV infection by an FDA approved method of detection

Laboratory Criteria documented any time during screening, prior to enrollment:

20. Negative PCR for malaria (except Group 6)
21. Negative sickle cell screening test (except Group 6)
22. Electrocardiogram (ECG) without clinically significant abnormalities (examples may include: pathologic Q waves, significant ST-T wave changes, left ventricular hypertrophy, any non-sinus rhythm excluding isolated premature atrial contractions, right or left bundle branch block, advanced A-V heart block). ECG abnormalities determined by a cardiologist to be clinically insignificant as related to study participation do not preclude study enrollment (except Group 6)
23. No evidence of increased cardiovascular disease risk; defined as >10% five-year risk by the non-laboratory method [23] (except Group 6)

Criteria Specific to Women:

24. Postmenopausal for at least 1 year, post-hysterectomy or bilateral oophorectomy, or if of childbearing potential:
    a. Negative beta-human chorionic gonadotropin (β-HCG) pregnancy test (urine or serum) on day of enrollment, and prior to product administration and CHMI, and
    b. Agrees to use an effective means of birth control through the duration of study participation

4.1.2. Exclusion Criteria

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

25. Woman who is breast-feeding or planning to become pregnant during study participation
26. Previous receipt of a malaria vaccine or anti-malaria monoclonal antibody
27. History of malaria infection
28. Any history of a severe allergic reaction with generalized urticaria, angioedema or anaphylaxis prior to enrollment that has a reasonable risk of recurrence during the study
29. Hypertension that is not well controlled
30. Receipt of any investigational study product within 28 days prior to enrollment/product administration (Note: SARS-CoV-2 vaccines approved by emergency use authorization are not exclusionary)
31. Receipt of any live attenuated vaccines within 28 days prior to enrollment/product administration
32. Receipt of any vaccine within 2 weeks prior to enrollment/product administration
33. Bleeding disorder diagnosed by a doctor (e.g. factor deficiency, coagulopathy, or platelet disorder requiring special precautions) or significant bruising or bleeding difficulties with intramuscular injections or blood draws
34. History of a splenectomy, sickle cell disease or sickle cell trait
35. History of skeeter syndrome or anaphylactic response to mosquito-bites (except Group 6)
36. Known intolerance to chloroquine phosphate, atovaquone or proguanil (except Group 6)
37. Use or planned use of any drug, including antibiotics, with antimalarial activity 4 weeks prior to CHMI (except Group 6)
38. History of psoriasis or porphyria, which may be exacerbated after treatment with chloroquine (except Group 6)
39. Anticipated use of medications known to cause drug reactions with chloroquine or atovaquone-proguanil (Malarone) such as cimetidine, metoclopramide, antacids, and kaolin (except Group 6)
40. History of Sjogren's syndrome

41. History of chronic or recurrent salivary gland disorder diagnosed by a clinician (note: an isolated occurrence of parotitis, sialadenitis, sialolithiasis, or of a salivary gland tumor is not exclusionary)
42. History of therapeutic head or neck radiation
43. Any other chronic or clinically significant medical condition that in the opinion of the investigator would jeopardize the safety or rights of the volunteer, including but not limited to: diabetes mellitus type I, chronic hepatitis; OR clinically significant forms of: drug or alcohol abuse, asthma, autoimmune disease, infectious diseases, psychiatric disorders, heart disease, or cancer

4.2. Inclusion of Vulnerable Subjects

4.2.1. Children

Children are not eligible to participate in this clinical trial because the study product has not been previously evaluated in adults. If the product is assessed as safe for further study, other protocols specifically designed for children may be conducted.

4.2.2. Adult Subjects who Lack Capacity to Consent to Research Participation

Adults who are unable to provide initial informed consent are excluded to enroll. Also, adults who permanently lose the capacity to provide on-going consent after initial consent and during the study will be discontinued from protocol participation as it is described in Section 4.6.

4.2.3. NIH Employees

NIH employees and members of their immediate families may participate in this protocol. We will follow the Guidelines for the Inclusion of Employees in NIH Research Studies and will give each employee a copy of the "NIH FAQs for NIH Staff Who are Considering Participation in NIH Research" published by Office of Human Research Subjects Protections on Research Involving NIH Staff as Subjects, Policy 404. For NIH employee subjects, consent will be obtained by an individual who is independent of the employee's team. If the individual obtaining consent is a co-worker to the subject, independent monitoring of the consent process will be included through the Bioethics Consultation Service. Protocol study staff will be trained on obtaining potentially sensitive and private information from co-workers or subordinates.

4.3. Clinical Procedures and Evaluations

Evaluation of study product safety will include laboratory studies, medical history, physical assessment by clinicians, and subject self-assessment. The study schedule is presented in the Schedule of Evaluations, APPENDIX I. Total blood volume drawn from each subject will not exceed the NIH Clinical Center Guidelines. In response to the coronavirus disease 2019 (COVID-19) pandemic and changing information related to testing, all NIH CC epidemiologic and testing guidelines will be followed during study conduct.

4.3.1. Recruitment and Retention

Study enrollments will be conducted at the NIH Clinical Center. Study subjects will be recruited through on-site and off-site IRB-approved advertising done through the VRC's screening protocol, VRC 500 (NCT 01375530). Effort will be made to include women and minorities in proportions similar to that of the community from which they are recruited. All volunteer facing materials used for recruitment and other purposes will be submitted to the IRB and approved before use.

a. Costs

There are no costs to subjects for their participation in this trial.

b. Compensation

Subjects will be compensated for time and inconvenience in accordance with the standards for compensation of the Clinical Research Volunteer Program. Compensation for study visit that includes IV product administration is $430; study visit that includes SC or IM product administration is $375. If enrollment occurs on a different day than study product administration, then visit compensation will be $85. Compensation will be $200 for scheduled follow-up visits that include venipuncture, $85 for clinic visits that do not include venipuncture, and $25 for timely completion of the electronic diary card. Compensation for a CHMI visit including the pre-CHMI clinic visit and activities is $455.

The total amount of compensation varies depending upon group and the visits completed. Compensation may also vary depending upon the number of days required for the daily evaluations in the period after a CHMI as those who become parasitemic early will require fewer days of in-clinic evaluation visits than those who have delayed or no parasitemia. CHMI control subjects will be compensated similarly for comparable visit types.

4.3.2. Screening

All screening procedures for this study will be completed through the VRC's screening protocol, VRC 500 (NIH 11-I-0164). The Recruitment Plan per NIH Policy 302 can be found in the NIH IRB approved VRC 500 protocol. Subjects will be recruited through Institutional Review Board (IRB)-approved advertising. Screening evaluations are performed to confirm eligibility and will include medical history review, physical exam, and the clinical laboratory tests detailed in APPENDIX I. Women presumed to be of reproductive potential will be given a pregnancy test. A baseline electrocardiogram (EKG) will be performed. Information related to recurrent or persistent dry mouth or swelling of salivary glands will be reviewed during screening per exclusion criteria. Additional assessments of health may be conducted at screening under protocol VRC 500 based on clinical judgment; no screening procedures will be done under protocol VRC 614. Pre-exposure research blood samples may be collected anytime during screening through enrollment and will not be subject to the "56-day prior to enrollment" restriction.

Informed consent documents will be reviewed during screening. Counseling related to potential risks of the study product, pregnancy prevention, and avoiding exposure to malaria will be performed. An Assessment of Understanding (AoU) will be completed in association with

enrollment into VRC 614. Records will be kept documenting the reason that screened subjects do not enroll.

Subjects who are not up to date on standard vaccinations may receive these, if available, during their participation in the screening protocol or at a later date during study participation.

4.3.3. Enrollment and Study Day 0

In this study, enrollment is defined as the assignment of a study identification number and a study group in the clinical database. A clinician will discuss the target dates and timing of the study product administration, CHMI, and sample collections before completing an enrollment to help ensure that the subject can comply with the projected schedule. Informed consent must be obtained prior to enrollment. For L9LS recipients, enrollment will occur at Visit 01R (Day -28 to Day 0) and may occur on the same day as product administration at Visit 02 (Day 0) in advance of product administration. For CHMI control subjects, Visit 01R (Day -56 to Day -1) is the enrollment day, which will be within 56 days prior to the CHMI.

For L9LS recipients, Day 0 is defined as the day of product administration. If Day 0 does not coincide with enrollment, then the enrollment day may be referred to by a negative number of days (i.e., Day -1). For calculating elapsed days following Day 0, each subsequent calendar date is labeled by the next sequential "Study Day" as shown in APPENDIX I. Since there may be more than one research sampling timepoint of interest per study day, each sample collection timepoint has its own "Visit Number." For this reason, there may be more than one visit number recorded on the same calendar date.

The study will start with subject enrollment directly into Group 1. Additional dose groups (Groups 2, 3, 4) will open per the dose escalation rules as outlined in Section 4.5, and subjects will be directly enrolled into the subsequent open groups. Subjects in Group 5 will be able to choose to participate in the control group and undergo CHMI without receiving product administration. In case of Group 5 dropouts prior to CHMI, replacement of control subjects and enrollment of a sufficient number of backup subjects is allowable to ensure a total of 6 subjects can serve as controls on the day of CHMI. Subjects in Group 6 will be enrolled after enrollment in all other groups is complete. Because this is an open-label design, subjects will know what group they are in on the day of enrollment.

Medical history and Day 0 evaluations (prior to product administration, as applicable per study group) are the baseline for subsequent safety assessments except that the screening evaluations will be the baseline for those only done at screening.

4.3.4. Product Administration

All product administrations will be completed according to the assigned group.

On the day of, and prior to product administration, vital signs (temperature, blood pressure, heart rate and respiratory rate) will be recorded, a targeted physical examination (based on signs, reported symptoms or interim medical history) may be conducted as needed, and women of childbearing potential must have a negative pregnancy test.

If a subject is assigned to an IV administration group, the IV access will be placed in an arm vein in an aseptic manner. A different site may be used for collection of PK blood samples; however, the same site may be used after flushing the line if another site is not available. L9LS will be

administered with approximately 50-120 mL of normal saline IV over about 15-30 minutes, with a target of 30 minutes. Infusions lasting longer than 30 minutes are allowed. If the subject experiences side effects during the infusion, the rate of infusion may be slowed or stopped to alleviate the symptoms.

If a subject is assigned to a SC administration group, the SC administration site(s) to be used must be assessed as acceptable by the clinician and the subject. The preferred SC administration site is the abdomen, but the upper arm or thigh may be used. Given the weight criterion in this study, the maximum volume needed to administer a 5 mg/kg SC dose is not expected to exceed 3.83 mL. The SC dose will be administered by standard needle in a maximum volume of about 2.5 mL per injection site. Up to two (2) SC injection sites may be used if deemed necessary by the clinician. SC administration sites should be at least 2 inches apart.

If a subject is assigned to a IM administration group, the IM administration site(s) to be used must be assessed as acceptable by the clinician and the subject. Injections will be administered into the deltoid muscle or quadriceps muscle. Given the weight criterion in this study, the maximum volume needed to administer a 5 mg/kg IM dose is not expected to exceed 3.83 mL. The IM dose will be administered by standard needle in a maximum of 1.0 mL per injection site. Up to four (4) IM injection sites may be used if deemed necessary by the clinician. IM administration sites should be at least 2 inches apart

4.3.5. Post-Product Administration Follow-up

In all study groups, the first subject in each dose group to receive a unique dose level (1, 5, or 20 mg/kg) will be observed for at least 2 hours following completion of product administration. All other subjects will be observed for at least 1 hour following completion of product administration. Collection of PK samples will be conducted according to the Schedule of Evaluations for the subject's study group.

Prior to discharge from the clinic, subjects will be assessed for local and systemic reactogenicity and vital signs will be recorded. Any subject who is assessed as being unwell or has ongoing reactogenicity symptoms will be asked to remain in the clinic until evaluation and discharge by a study clinician. This includes the possibility of an overnight inpatient stay to evaluate for safety.

4.3.6. Solicited Adverse Events (Reactogenicity)

Each subject will be given a 7-day diary (paper and electronic-based available), a thermometer, and a measuring device. Subjects will use the diary to record their highest temperature, local and systemic symptoms, and concomitant medications daily for 7 days after each product administration. Subjects will be provided training on diary completion and proper usage of the thermometer to measure temperature and the measuring device to measure injection site symptoms. Completion of diary training will be noted in the source documents. While the electronic diary is preferred, subjects will have the option to use a paper diary. The paper diary, if used, will be transcribed into the study database and stored in the subject file for monitoring purposes. When neither paper nor electronic diary is available from the subject, the study clinician will document the source of reactogenicity information recorded in the study database.

The signs and symptoms solicited by the diary will include systemic events of temperature, feeling unusually tired or unwell, muscles aches, headache, chills, nausea, and joint pain, and local events at the product administration site of pain/tenderness, swelling, redness, bruising, and

pruritus. Subject diaries will be reviewed by a clinician for accuracy and completeness at follow-up visits. Clinicians will follow any solicited symptoms that are ongoing after 7 days until they have resolved.

Diary data will be available in real-time to clinicians for subjects who use the electronic diary. Subjects using a paper diary will be encouraged to contact the clinic as soon as possible for any moderate or severe side effects that they experience in the 7 days post product administration. A study clinician may contact the subject by phone if any moderate or severe side effect is reported. Events that may require a clinic visit include rash, urticaria, fever of 38.6˚C (Grade 2) or higher lasting greater than 24 hours or significant impairment in the activities of daily living (such as those consistent with Grade 2 or higher impairment). Additionally, other clinical concerns may prompt a study visit based on the judgment of a study clinician.

4.3.7. CHMI Procedures

The interval between administration of study product and CHMI will vary depending on when a subject is enrolled. The CHMI will only occur following an evaluation of Day 7 safety data post product administration and may be administered at any time ≥ 8 days through 12 weeks post product administration. Some flexibility around the interval between the time of L9LS administration and CHMI is permitted given the need to work with each subject's personal schedule, availability of the CHMI facility and post-CHMI follow-up.

Prior to scheduling the CHMI, at least two emergency contact numbers will be confirmed and verified as authentic for each subject who will participate in the challenge. The clinical study team will review each subject's adherence to the schedule and safety follow-up to date. This review will attempt to identify any likelihood of unreliability on the part of the subject during the CHMI phase of the study. Any subject expressing inability to comply with study requirements may be deemed unsuitable for CHMI and will be excluded from the CHMI phase of the study. Any subject who receives study product, however, will be encouraged to remain in the study for safety follow-up visits.

Women of childbearing potential must have a negative pregnancy test within 2 days prior to CHMI. Use of antibiotics by CHMI participants should be avoided at least 4 weeks prior to and during the CHMI unless medically warranted.

Prior to CHMI procedure on the day of CHMI, vital signs will be recorded for subjects participating in the CHMI. An abbreviated physical examination will be performed by an Advanced Practitioner to confirm the subject's ability to participate in the CHMI procedure.

CHMI will be conducted by experienced insectary and clinical staff. Mosquitoes infected via membrane feeds in preparation for the CHMI contain sporozoites in their salivary glands and up to 5 at a time will be allowed to feed on each subject under controlled conditions. Following exposure, the mosquitoes will be immediately dissected to confirm the presence of a blood meal and to determine the infectivity rate and the salivary gland score. Additional mosquitoes will be allowed to feed until 5 bites showing presence of a blood meal and a minimum 2+ salivary gland score has been achieved for each subject.

Prior to discharge from CHMI, subjects will be observed for a minimum of 30 minutes. Vital signs will be taken and the mosquito bite site will be assessed. Subjects will be given an Emergency Notification card and will also be supplied with Hydrocortisone cream. They will

also be provided with counseling and written recommendations to reduce risk of natural mosquito exposure beginning 5 days after CHMI and continuing until completion of treatment.

4.3.8. Post-CHMI Follow-Up

The study team will be in contact with subjects at least 2 times in the first 7 days after the CHMI to provide close monitoring of clinical status. Blood samples to evaluate for malaria parasitemia will be collected daily and run on PCR from days 7 through 17 with a final PCR performed at day 21 post-CHMI. Malaria PCR testing is processed in the morning and results are available the same day. If the result is positive for malaria, the subject will be contacted by phone immediately. Subject will be asked to return to the clinic within two hours of notification to initiate malaria treatment. Prior to Day 21, regular parasitemia evaluations will stop after treatment is initiated for positive cases of parasitemia. In the absence of malaria infection, all subjects who have not already started treatment will be provided with directly observed definitive antimalarial treatment at Day 21.

During the post-CHMI follow-up period, subjects may participate in their normal daily activities. A study clinician will be available 24 hours a day by telephone or in person to the site staff in case consultation about subject's signs and symptoms is needed. Any subject who is assessed as being unwell during the post-CHMI follow-up will be asked to remain in the clinic until evaluation and discharge by a study clinician. This includes the possibility of an overnight inpatient stay for evaluation.

4.3.9. Parasitemia Management

Following CHMI, a case of malaria parasitemia will be defined as either a single positive PCR result or a thick blood smear that meets the criteria for positivity. PCR allows for cases of malaria to be identified before gametocytes can develop and thus before detection of gametocytes by blood smear are detectable. Malaria infection will be treated when the criterion for a case is met.

Regardless of PCR or blood smear results, all CHMI participants will receive directly observed antimalarial treatment at Day 21 post CHMI, if they have not already been treated for parasitemia by this timepoint. Subjects may also be provided with treatments like antiemetics and ibuprofen as needed for management of symptoms.

Refer to the Schedule of Evaluations, APPENDIX I**,** for the safety laboratory evaluations that are required to be performed at the onset of treatment and about 2 days later.

Malaria infections in all subjects will be treated promptly and administered as directly observed therapy (DOT) by a clinician until the specified course of treatment. Treatment regimens subsequently described are known to be effective against the Pf strain being used in the CHMI.

- First line of treatment: a standard atovaquone/proguanil (Malarone®) regimen:

  Four Malarone Tablets (adult strength tablet = 250 mg atovaquone/100 mg proguanil; total daily dose 1 g atovaquone/400 mg proguanil hydrochloride) taken as a single dose daily for 3 consecutive days with food or a milky drink.

- Alternative treatment: a standard chloroquine regimen:

  Total of 1500 mg chloroquine base (2500 mg salt) given orally in divided doses: 600 mg base (1000 mg salt) initially, followed by 300 mg base (500 mg salt) given 6, 24, and 48 hours later]

Alternative medications and regimens known to be effective in curing the Pf strain administered for the CHMI may be used in the event of allergies, intolerances or lack of availability of treatments listed above.

Following treatment for a positive case of malaria, cure will be documented by a PCR negative result at 26 days (± 5 days) after the completion of treatment. Subjects who remain PCR negative will be contacted by phone at 26 (days ±5 days) after last negative PCR.

4.3.10. Follow-Up through End of Study

Study follow-up will continue via clinical visits through 24 weeks after the product administration or 8 weeks post final CHMI, whichever is most stringent. The visit schedule is based on intervals of time after product administration or CHMI. The schedule of visits, allowable windows for completing the visits, and evaluations performed at each visit are shown in the Schedule of Evaluations, APPENDIX I. Out of window study visits will be discouraged and recorded as protocol deviations but may be permitted at the discretion of the PI in the interest of obtaining safety and PK evaluations following exposure to the investigational study product or conduct of a CHMI.

Any subject who receives investigational product will be required to follow the product administration schedule for a complete safety and research evaluation through study duration. Subjects who undergo CHMI will be required to follow the CHMI Schedule of Evaluations to completion. When visits from both schedules occur on the same day, all required components of the required visits for each schedule must be completed.

Subjects who receive study product but do not receive CHMI as scheduled are expected to continue follow-up according to the schedule for IV, SC, or IM group through 24 weeks, except that research sample collections may be discontinued for pregnant women or others in which it is contraindicated.

Refer to Section 4.6 for criteria for discontinuing product administration and/or study participation.

4.4. Concomitant Medications

Only routine prescription medications will be entered in the database at the time of enrollment. Subsequently, concomitant medications are only updated or recorded in the study database if there is an occurrence of an adverse event (AE) that requires expedited reporting, a change to pre-existing condition treatment, or the development of a new chronic condition that requires ongoing medical management. Treatment with antimalarial drugs will be recorded on a Malaria Endpoint Case Report Form (CRF). 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 study database.

4.5. Dose Escalation Plan

This study will include a series of interim safety reviews to assess product safety in a stepwise manner. The activation of additional dose groups will proceed in a staged manner that is governed by the outcome of the planned interim PSRT data reviews. The PSRT must assess the data as showing no significant safety concerns before proceeding with group activation. If there are discontinuations from the study before there are sufficient data to conduct the dose escalation review for a specific group, then additional subjects may be enrolled to complete the dose evaluation.

The study will begin with direct enrollment of subjects into Group 1, with one subject enrolled per day for the first 3 subjects. The first dose escalation review (from 1 mg/kg IV to 5 mg/kg IV) will occur when 3 subjects who received the 1 mg/kg dose by IV have completed the Day 7 safety follow-up visit. The PSRT review will determine whether enrollment into Group 2 may begin.

The second dose escalation review (from 5 mg/kg IV to 20 mg/kg IV) will occur when 3 subjects who received the 5 mg/kg dose by IV have completed the Day 7 safety follow-up visit. The PSRT review will determine whether enrollment into Group 4 may begin.

Group 3 (5 mg/kg SC) can enroll at any time and is not contingent upon the dose escalation reviews for the IV doses.

If there are discontinuations from the study before there are sufficient data to conduct the dose escalation review for a specific group, then additional subjects may be enrolled to complete the dose evaluation. Additionally, AEs assessed as related to study product at the time of a dose escalation review may warrant enrollment of additional subjects into a dose group to reassess safety before proceeding to a higher dose. Consultation with the IRB or FDA as per study pause criteria may occur if indicated.

Group 6 (5 mg/kg IM) was added after completion of the dose escalation process and can enroll at any time.

4.6. Criteria for Discontinuation of Protocol Participation

All participants who received the study product will remain on study and continue safety follow-up to Visit 14 (i.e., week 24). Participants who have completed the CHMI, but did not receive study product, will remain on study and continue safety follow-up to Visit C18. Decisions by the PI or designee to discontinue a subject from protocol participation will be made with the following criteria.

4.6.1. Discontinuation from Protocol Participation

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

1. Subject voluntarily withdraws;
2. Subject is lost to follow-up

4.7. Criteria for Pausing and Resuming the Study

The study team will closely monitor and review study data as they become available to make determinations regarding the presence, severity and attribution of AEs. Study product administrations and new enrollments will be paused if any of the following criteria are met:

- **One** (or more) subject experiences a **SAE** that is assessed as related (possibly, probably or definitely) to the study product, or
- **Two** (or more) subjects experience the same **Grade 3 or higher AE** that is assessed as related (possibly, probably or definitely) to the study product (other than self-limited Grade 3 solicited reactogenicity).

4.7.1. Plan for Review of Pauses and Resuming Rules

In the event of a pause, the IND Sponsor Medical Officer (MO) and the PSRT will be promptly notified. The IND Sponsor MO and PI, in consultation with the PSRT, will conduct a review of available information, including the events that lead to the pause, and will make the decision to resume, amend or close the study. As part of the pause review, the reviewers may also advise on whether the study needs to be paused again for any subsequent events of the same type.

Study product administrations and new enrollments would resume only if review of the AEs that caused the pause results in a recommendation to permit further study product administrations and study enrollments. Safety data reports and changes in study status will be submitted to relevant regulatory authorities in accordance with Section 5 and institutional policy.

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 subject's participation in research, whether or not considered related to the subject's participation in the research. In the context of FDA-required reporting, an AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

- Solicited AEs (i.e., reactogenicity parameters as defined in Section 4.3.6) will be recorded without attribution assessments by the subject on paper or an electronic diary for 7 days after each product administration.
- Unsolicited AEs will be recorded in the study database with attribution assessments during the following periods:

  1) from product administration through the Day 28 post-product administration visit; and

  2) from CHMI through the Day 28 post-CHMI visit.

After and between the indicated time periods, only SAEs (as detailed in Section 5.3) and new chronic medical conditions will be recorded as AEs through the last expected study visit or contact.

Malaria and the associated signs and symptoms of parasitemia events occurring at any time during the study will be recorded on a Malaria Endpoint CRF and will not be recorded as an AE.

APPENDIX II describes how attribution assessments, the relationship between an AE and the study product, CHMI or both, will be determined. Also available in APPENDIX II is the link to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1 [July 2017], which will be used to determine the severity grades of AEs in this protocol with several modifications as noted.

5.2. Serious Adverse Events

The term "Serious Adverse Event" (SAE) is defined in 21 CFR 312.32 as follows: "An adverse event or suspected adverse reaction is considered serious if, in the view of either the investigator or the 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 or suspected adverse reaction that represents an immediate risk of death to the subject. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death. Similarly, a hospital admission for an elective procedure is not considered a SAE.

5.3. Adverse Event Reporting to the IND Sponsor

AEs that meet SAE criteria must be reported and submitted by the clinical site on an expedited basis to the IND Sponsor, VRC/NIAID/NIH, according to sponsor guidelines as follows:

- Results in death;
- Is life threatening (places the subject at immediate risk of death from the event as it occurred);
- Results in inpatient hospitalization or prolongation of existing hospitalization;
- Results in a persistent or significant disability/incapacity;
- Results in a congenital anomaly/birth defect in the offspring of a study subject; OR
- Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the 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).

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

An investigator will communicate an initial SAE report within 24 hours of site awareness of occurrence to the IND Sponsor by data entry into the database, which triggers an alert to the IND Sponsor MO. Within 3 working days, a written summary by the investigator should be submitted to the IND Sponsor.

In order for the IND Sponsor to comply with regulations mandating sponsor notification of specified SAEs to the FDA within 7 and/or 15 calendar days, the investigator must submit additional information as soon as it is available.

5.4. IND Sponsor Reporting to the FDA

The IND Sponsor is responsible for making 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 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 per 21 CFR 312.32 as soon as possible but not exceeding 7 calendar days for unexpected

fatal or life-threatening events, and not exceeding 15 calendar days for other qualifying events. IND Safety Reports will also be provided to the IRB.

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

5.5. Reporting to the Institutional Review Board

The following information is consistent with NIH IRB Policy 801: Reporting Research Events, Version 1, effective July 1, 2019.

Reportable Event: An event that occurs during the course of human subject research that requires notification to the IRB.

For the purposes of this policy, reportable events include the following:

- Unanticipated Problems (UPs) involving risks to subjects or others
- Non-compliance (including major protocol deviations and noncompliance that is not related to a protocol deviation)
- Deaths related or possibly related to research activities
- New information that might affect the willingness of subjects to enroll or continue participation in the study

5.5.1. Unanticipated Problem

An Unanticipated Problem (UP) is defined as any incident, experience, or outcome that meets **all** the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied; **and**
- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); **and**
- Suggests that the research places subjects, or others (which may include research staff, family members or other individuals not directly participating in the research) at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or expected.

A UP must be reported within 7 calendar days of an investigator becoming aware of the actual or suspected UP.

5.5.2. Non-Compliance

Non-compliance is the failure of investigator(s) to follow the applicable laws, regulations, or institutional policies governing the protection of human subjects in research, or the requirements or determinations of the IRB, whether intentional or not.

Non-compliance may be unintentional (e.g. due to lack of understanding, knowledge, or commitment), or intentional (e.g. due to deliberate choice to ignore or compromise the requirements of any applicable regulation, organizational policy, or determination of the IRB).

Non-compliance is further characterized as serious or continuing as follows:

- Serious non-compliance – Non-compliance, whether intentional or not, that results in harm or otherwise materially compromises the rights, welfare and/or safety of the subject. Non-compliance that materially effects the scientific integrity or validity of the research may be considered serious non-compliance, even if it does not result in direct harm to research subjects.
- Continuing non-compliance – A pattern of recurring non-compliance that either has resulted, or, if continued, may result in harm to subjects or otherwise materially compromise the rights, welfare and/or safety of subjects, affect the scientific integrity of the study or validity of the results. The pattern may comprise repetition of the same non-compliant action(s), or different noncompliant events.

Any actual or suspected non-compliance by any investigator or entity associated with the protocol must be reported to the IRB by the PI/designee within 7 calendar days of any investigator or individual associated with the protocol first becoming aware.

5.5.3. Protocol Deviation

A Protocol Deviation (PD) is defined as any change, divergence, or departure from the IRB-approved research protocol and are further characterized as major and minor as follows:

- Major Deviations – Deviations from the IRB approved protocol that have, or may have the potential to, negatively impact, the rights, welfare or safety of the subject, or to substantially negatively impact the scientific integrity or validity of the study.
- Minor Deviations – Deviations that do not have the potential to negatively impact the rights, safety, or welfare of subjects or others, or the scientific integrity or validity of the study.

For the reporting purposes, failure of subjects to comply with the research protocol does not represent non-compliance unless that failure is due to an action or omission of a member of the research team, for example, the failure to give adequate instruction to the subject.

A major deviation must be reported within 7 calendar days of an investigator becoming aware of an actual or suspected deviation. Although PDs are also non-compliance, these should only be reported once as deviations. Major deviations resulting in death must be reported within 24 hours of the occurrence of the event or of any member of the study team becoming aware of the death.

Researchers are responsible for monitoring their studies throughout the year for adherence to the IRB approved protocol. The purpose of this monitoring is to identify major deviations and to look for trends in minor deviations that may indicate a systemic issue in how the study is being conducted that could potentially negatively impact the rights, safety, or welfare of participants or the study's ability to produce scientifically valid results. A series of minor deviations pointing toward a more global issue that could affect the rights, safety or welfare of the participant or

affect the validity of the study should be reported as a major deviation. In all other instances, a summary of minor deviations should be provided to the IRB at the time of continuing review.

5.5.4. Death

Any death of a research subject that is possibly, probably or definitely related to the research must be reported within 24 hours of an investigator becoming aware of the death.

5.5.5. New Information

New information that might affect the willingness of a subject to enroll or remain in the study should be reported within 7 calendar days of an investigator first becoming aware.

5.5.6. Suspension or Termination of Research Activities

Any suspension or termination of research activities, including holds on new enrollment, placed upon the research by the study sponsor, NIH or IC leadership, or any regulatory agency must be reported within 7 calendar days of an investigator becoming aware.

5.5.7. Expedited Reporting to the IRB

Death related to research must be reported within **24 hours**.

The following will be reported within **7 calendar days** of investigator awareness:

- Actual or suspected UPs;
- Actual or suspected non-compliance;
- Actual or suspected Major PDs;
- SAEs that are actual or suspected UPs;
- New information that might affect the willingness of a subject to enroll or remain in the study;
- Suspension or termination of research activities, including holds on new enrollment, placed upon the research by the study sponsor, NIH or IC leadership, or any regulatory agency.

5.5.8. Annual Reporting to the IRB

The following will be reported to the IRB in summary at the time of Continuing Review:

- Summary of UPs and non-compliance;
- AEs, including SAEs, that are not UPs, as a narrative summary statement indicating whether these events were within the expected range;
- Minor PDs (aggregate summary);
- Any trends or events which in the opinion of the investigator should be reported.

6. STATISTICAL CONSIDERATIONS

6.1. Overview

This study is a Phase 1, dose-escalation study in healthy adults to assess the safety, PK and protective efficacy of L9LS, an investigational human antimalarial mAb.

6.2. Sample Size and Accrual

Trial recruitment will target about 29 healthy adults, ages 18 to 50 years, as shown in Table 1. This includes 18 subjects that receive study product and then undergo CHMI and 6 controls who will only undergo the CHMI and do not receive study product and 5 subjects who will receive study product but not take part in the CHMI. The permitted accrual is 40 subjects in total (inclusive of 2 subjects who will serve as back-ups to the control) to allow for additional enrollments to meet the minimum number of subject evaluations needed for a dose-escalation evaluation or CHMI per protocol criteria. Dose escalation rules are described in Section 4.5. Specifically, if a subject enrolls into a study product group but does not receive a product administration or withdraws before the challenge for reasons that are not safety related, or a control group subject withdraws before the malaria challenge occurs, then additional subjects may be enrolled to achieve the accrual target. Following a withdrawal from a study product group, additional enrollments may be made if there is sufficient time to complete product administration prior to the scheduled CHMI.

The primary goal of this study is to identify safety concerns associated with L9LS at different doses. Primary sample size considerations 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 serious adverse events. With a sample size of n=5, there is over 90% chance to observe at least 1 SAE if the true rate is at least 0.370 and over 90% chance to observe no SAE if the true rate is no more than 0.020. With a sample size of n=23, there is over 90% chance to observe at least 1 SAE if the true rate is no less than 0.096 and over 90% chance of observing no SAE if the true rate is no more than 0.004. Probabilities of observing 0 or more than 1 SAE within a group are presented in Table 2 for a range of possible true event rates.

Table 2: Probability of Events for Different Safety Scenarios (n=5 or 23)

True Event Rate	n=5		n=23	
	Pr(0)	Pr(>1)	Pr(0)	Pr(>1)
0.005	0.975	0.000	0.891	0.006
0.01	0.951	0.001	0.794	0.022
0.02	0.904	0.004	0.628	0.077
0.035	0.837	0.011	0.441	0.192
0.05	0.774	0.023	0.307	0.321
0.1	0.590	0.081	0.089	0.685
0.15	0.444	0.165	0.024	0.88
0.2	0.328	0.263	0.006	0.96
0.3	0.168	0.472	0.000	0.997

Table 3 gives the upper and lower bounds for 95% exact binomial confidence intervals of the true SAE rate at possible numbers of events within a group. Within a group size of n=5, if none experience an SAE, the 95% exact confidence interval has an upper bound of 0.522. With a group size of n=23, if 2 subjects experience an SAE, the exact 95% confidence interval has a lower and upper bound of 0.011 and 0.28, respectively.

Table 3: 95% Confidence Intervals for the True Rate at Possible Observed Number of Events (n=5 or n=23)

Observed Number of Events	95% Confidence Interval (n=5)		95% Confidence Interval (n=23)	
	Lower Bound	Upper Bound	Lower Bound	Upper Bound
0	0.000	0.522	0.000	0.148
1	0.005	0.716	0.001	0.219
2	0.053	0.853	0.011	0.28
3	0.147	0.947	0.028	0.336
4	0.284	0.995	0.05	0.388
5	0.478	1.000	0.075	0.437
6			0.102	0.484
7			0.132	0.529
8			0.164	0.573
9			0.197	0.615

6.3. Statistical Analysis

Enrollment of L9LS recipients may occur on the same day as product administration at Visit 02 (Day 0) or in advance of product administration at Visit 01R (Day -28 to Day 0), except in the case of controls. All subjects who receive product administration will provide safety data.

Three analysis cohorts are involved in the statistical analysis:

- Intent-to-treat (ITT) - This cohort will include all enrolled subjects who receive product administration and will be analyzed according to the assigned group.
- As-treated - This cohort will include all enrolled subjects who receive product administration and will be analyzed according to the actual dose they receive.
- Modified intent-to-treat (mITT) – This cohort will include all enrolled subjects who participate in the CHMI challenge and will be analyzed according to the assigned group.

All statistical analyses will be performed using SAS and R statistical software.

6.3.1. Analysis Variables

The analysis variables consist of baseline, safety parameters, PK, and presence or absence of malaria infection after CHMI. Descriptive statistics will be used to summarize baseline characteristics, inclusive of demographics and safety laboratory measurements.

6.3.2. Safety Analysis

Safety evaluation will be performed using the as-treated cohort. The number and percentage of subjects with one or more AEs will be summarized by dose group along with the exact 95% confidence intervals of the AE rate. For subjects experiencing more than one AE, they will be counted once under the event of highest severity. In addition, a complete listing of AEs for each subject will provide details such as severity, duration, and relationship to study product. Summaries will be provided for any solicited or unsolicited AEs.

a. Solicited Reactogenicity

Solicited AE data will be collected after product administration. The number and percentage of subjects experiencing each type of solicited sign or symptom will be tabulated by severity and by dose group and overall (i.e., pooled IV dose groups and pooled SC and IV dose groups). Subjects with multiple occurrences of the same event will be counted once using the event of highest severity.

b. Adverse Events

All reportable AEs will be recorded and coded by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT). The number and percentages of subjects with each unsolicited AE will be tabulated by severity and relationship to the study product, and by dose group and overall (i.e., pooled IV dose groups and pooled SC and IV dose groups). Subjects with multiple occurrences of the same event will be counted once using the event of highest severity or strongest relationship to the study treatment.

A by-subject listing of all unsolicited AEs will provide details including severity, relationship to treatment type, seriousness, new medical condition status, onset and end date, duration, and outcome.

c. 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.

6.3.3. Pharmacokinetics Analysis

PK analysis will be performed using the as-treated cohort. Blood samples for PK evaluations will be collected at defined time-points as listed in APPENDIX I.

Individual Subject Pharmacokinetic Analysis: A non-compartmental (NC) PK analysis will be performed using Phoenix 7.0 (Certara^{R}), PKPlus or a similar program on the L9LS concentration data generated from each subject. Individual subject and dosing group concentration vs time profiles will be constructed in linear and semi-log scales. In the NC analysis the maximum concentration (Cmax) and time of maximal concentration (Tmax) will be taken directly from the observed data. The area under the concentrations vs. time curve (AUC) will be calculated using the trapezoidal method and determined out to the final concentration collected. If a subjects L9LS concentration falls below the quantitative limit (QL) of the assay before the final of PK sample collection, the sample with concentration below the QL will be assigned a L9LS concentration value of "0" for AUC calculations. Later PK samples after the

initial concentration below the QL sample will be ignored in AUC calculations because partial AUC is not contributory to the total AUC. In addition to calculation of the total AUC from Time=0 to the last L9LS concentration ($AUC_{0\text{-last}}$), Time= 0 to the CHMI challenge ($AUC_{0\text{-CHMI}}$) and Time of CHMI to 21 Days post CHMI ($AUC_{CHMI\text{-}21DCHMI}$) will be determined. The time weighted average concentrations (Cave) during these intervals will be calculated as the AUC divided by the AUC collection interval, e.g. $Cave_{CHMI\text{-}21DCHMI}$ = ($AUC_{CMHI\text{-}21DCHMI}$) / 3weeks. The terminal slope, λ_z will be determined by regression of the terminal, log-linear portion of the concentration vs. time profile. If the final PK sample has measurable L9LS concentrations greater than the assay QL, the AUC post final PK collection ($AUC_{last\text{-}infinity}$) will be estimated as C_{last}/λ_z and $AUC_{0\text{-}infinity}$ will be calculated as sum $AUC_{0\text{-last}}$ + $AUC_{last\text{-}infinity}$.

Population Pharmacokinetic Analyses: Population PK analyses will be performed on the PK data following IV and SC administration to determine compartmental PK parameters with the PK program NONMEM 7.3 or later (ICON^R). Based on preclinical PK results for L9LS and known PK behavior studies of mAbs, two-compartment model will be used (subroutine ADVAN4 TRANS4). Both zero order and first order absorption following SC administration will be evaluated and a lag time included if a delay is seen in the raw data figures. The First Order Conditional Estimation Method with Interaction (FOCEI) will be used. The population analysis will generate estimates for clearance (CL) central and peripheral volumes of distribution (Vd_1 and Vd_2), inter-compartmental clearance (Q), CL and SC bioavailability (F). Total volume of distribution at steady-state (Vdss), will be calculated as the sum of Vd_1 + Vd_2. Alpha and beta half-lives will be calculated from CL, Q, Vd_1 and Vd_2 using standard equations [24]. While the number of subjects is expected to be sufficient to characterize the typical PK parameters and their between-subject variabilities (BSVs), the sample number is too small for a robust broad population PK covariate analysis. Therefore, the impact of subjects' size will be accounted for using allometric scaling normalized to 70 kg with dose level and CHMI response being the only covariates explored. Individual subjects' empiric Bayesian PK parameter estimates will be generated using the *posthoc* subroutine and may be used to estimate individual participant L9LS concentration-time profiles.

Final model selection will be based on changes in the objective function, a goodness-of-fit statistic generated by NONMEM, and graphically by goodness of fit plots. The final population PK model will be assessed using bootstrap analysis. Dosing strategies and their ability to achieve and maintain target L9LS concentrations will be performed using the final population PK model and Monte Carlo simulations with at least 1000 replicates.

6.3.4. Efficacy Analysis

Efficacy analysis will be performed using the mITT cohort. The primary efficacy analysis will be based on a two-sided Barnard test on the proportion of infected subjects who receive L9LS compared to the controls who undergo CHMI concurrently. The secondary efficacy analyses will be based on time-to-parasitemia, where L9LS recipients will be compared with the control participants via a log-rank test. Kaplan-Meier curves will also be provided for each group.

To assess how L9LS concentration impacts protection against infection, a logistic regression may be performed to estimate the infection risk as a function of the L9LS concentration at the time of challenge. For the same reason, a Cox proportional hazards regression may be

performed to estimate the hazard function with the L9LS concentration at the time of challenge and $Cave_{CHMI\text{-}28DCHMI}$, as a regressor.

In addition to the above efficacy analyses, descriptive statistics will be provided which include the proportion of infection post CHMI in each dose group and the control group. To assess the comparability of challenge, salivary gland score (related to the quantity of sporozoites in each mosquito) will be listed for each participant and the summary statistics, such as the median and interquartile range of the salivary gland score, will be reported for each dose group as well as the control group.

6.3.5. Interim Analyses

PK data may be analyzed for each dose group. Preliminary PK analyses may be performed per dose level prior to CHMI which may only generate a subset of the final PK parameters.

7. PHARMACY PROCEDURES

The study groups are shown in Table 1.

7.1. Study Product

VRC-MALMAB0114-00-AB (L9LS) is a sterile, aqueous, buffered solution filled into single dose vials at 150 + 15 mg/mL in a formulation buffer composed of 10 mM Acetate Phosphate, 10 mM Sodium Chloride, 250 mM Proline, 0.02% Polysorbate 80 at pH 5.6; and to a target fill volume of 2.25 ml in a 3 ml vial. The drug product container closure system consists of Type I glass vials, chlorobutyl rubber stoppers, and seals purchased from approved manufacturers.

7.2. Storage and Temperature Excursions

Filled product must be stored at -35°C to -15°C, in a qualified, continuously-monitored, temperature-controlled freezer.

The site pharmacist must promptly report any storage temperature excursions outside of the normal allowance to the IND Sponsor. The affected product must be quarantined in a separate area under protocol-specific temperature ranges until further notice from the Sponsor. If the excursion results in thawed material, DO NOT REFREEZE; store the thawed, vialed material at 2°C to 8°C.

When a storage/shipping/handling excursion occurs, the IND Sponsor designee must send a notification of the occurrence of an excursion to VRCProductinquiries@nih.gov. An automatic email reply will be sent to the notifier, including (as an attachment) the Clinical Excursion Reporting Form, which can be filled electronically (or manually and scanned, if needed). The completed form and relevant attachments (e.g. temperature charts) must be emailed to the VRC via the same email address (VRCProductinquiries@nih.gov) using the "reply" function. The IND Sponsor will notify the site pharmacist if continued clinical use of the product is acceptable or will provide further instructions.

7.3. Labeling of Study Product Vial

Vials of study product will be individually labeled with the name of the material, volume, lot number, concentration, storage instructions, Investigational Use Statement ("Limited by Federal Law to Investigational Use"), and manufacturer information.

7.4. Preparation of Study Product for Administration

This section describes how to prepare study injections and will be updated when information is available. For complete and detailed instructions for the preparation of the product please see Appendix III.

7.4.1. Preparation for IV Administration

For each IV infusion order, the subject's weight, dose level, and study group code will be included in the pharmacy order. To prepare an IV infusion, the pharmacist will: 1) calculate the total milligrams of L9LS needed, 2) retrieve the minimum number of thawed vials required to prepare the full dose, 3) withdraw the necessary amount of L9LS, and 4) add this volume to a

normal saline IV bag using sterile compounding techniques to maintain sterility. Overfill may be added to the IV bag to ensure proper IV administration via a volumetric pump when the total volume to be administered is low (e.g. less than 50 mL). The ideal L9LS concentration in the final product to be infused is greater than 2 mg/mL in order to maintain appropriate formulation.

Thaw and equilibrate vials for a minimum of 1 hour and 30 minutes at ambient temperature. If thawed vials are removed from 2°C to 8°C, equilibrate at ambient temperature for a minimum of 30 minutes. Prior to preparation for administration in the IV bag, vials should be gently swirled for approximately 30 seconds while avoiding foaming. DO NOT SHAKE THE VIALS.

An in-line filter infusion set must be used for IV product administrations and MUST comply with the following specifications: 1.2-micron PES (polyethersulfone) filter membrane, DEHP-free, latex-free (equivalent to B.Braun #473994 filter extension set). When the in-line filter is added to the tubing, the administration set must then be primed.

The study product solution will typically be administered IV over about 15-30 minutes using a volumetric pump. The total time needed to administer the dose may be longer than 30 minutes based on factors such as subject tolerance. The mL/hr infusion rate may vary based on the total volume needed to administer a full dose.

At the end of product administration, the IV administration set must be flushed with about 30 mL (or appropriate volume) of normal saline unless the IV bag was prepared with overfill.

7.4.2. Preparation for SC or IM Administration

For each SC or IM administration order, the subject's weight, dose level, and study group code will be included in the pharmacy order. To prepare a SC or IM administration dose, the pharmacist will calculate the total mg needed and retrieve the minimum number of vials needed to prepare the full dose. Thaw and equilibrate vials for a minimum of 1 hour and 30 minutes at ambient temperature. If thawed vials are removed from 2°C to 8°C, equilibrate at ambient temperature for a minimum of 30 minutes. Prior to preparation for administration, vials should be gently swirled for approximately 30 seconds while avoiding foaming. DO NOT SHAKE THE VIALS.

The needed volume of L9LS must be withdrawn from the vial into 1 to 4 syringes using a 5-micron filter needle. A new filter needle must be used for each syringe. The filter needle must be discarded prior to dispensing and replaced with a needle suitable for SC or IM injection at the time of administration. The product may be administered by direct SC or IM injection with needle and syringe. The clinician will use proper SC or IM technique to ensure administration into SC fatty layer or the IM injection into muscle and a slow push to minimize discomfort or the excessive distention of overlying skin.

7.4.3. Handling of Prepared Product for IV, SC, or IM Administration

After product preparation in an IV bag, the prepared L9LS may be stored at 2°C to 8°C for a maximum of 24 hours and/or at ambient temperature for a maximum of 4 hours total including the infusion time. Product may not be stored in direct sunlight.

After preparation in syringes for SC or IM administration, the prepared L9LS may be stored at 2°C to 8°C up to 24 hours and/or at ambient temperature up to 4 hours. Product may not be stored in direct sunlight.

7.5. Study Product Accountability

The study pharmacist or designee will be responsible for maintaining an accurate record of the study group codes, inventory, and an accountability record of study agent supplies. Electronic documentation as well as paper copies may be used.

7.6. Study Product Disposition

The empty vials and the unused portion of a vial will be discarded in a biohazard containment bag and incinerated or autoclaved in accordance with the institutional or pharmacy policy. Any unopened vials that remain at the end of the study will be returned to the production facility or discarded at the discretion of the sponsor in accordance with policies that apply to investigational agents. Partially used vials will not be administered to other subjects or used for *in vitro* experimental studies. These vials will be disposed of in accordance with institutional or pharmacy policy.

8. HUMAN SUBJECT PROTECTIONS AND ETHICAL OBLIGATIONS

This research will be conducted in compliance with the protocol, International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and all applicable regulatory requirements.

8.1. Institutional Review Board

The protocol, proposed informed consent form, other written subject information, and any proposed advertising material will be submitted to the IRB for review and written approval.

The investigator must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent document. The investigator will notify the IRB of research events that occur on study as described in Section 5.5.

The investigator will be responsible for obtaining IRB approval of the annual Continuing Review throughout the duration of the study.

8.2. Informed Consent

The study informed consent form (ICF) is provided as a separate hard copy and describes the investigational product to be used and all aspects involved in protocol participation.

The PI or designee is responsible for obtaining written informed consent from the subject after adequate explanation of the aims, methods, anticipated risks and benefits of the study and before any protocol-specific procedures or study product is administered. The AoU will be completed before the study ICF is signed.

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 the person who conducted the informed consent discussion. The signed ICF will be retained in the medical chart and a copy of the ICF will be provided to the subject.

During the consent process, participants and investigators will view the same approved consent document simultaneously in their respective locations.

8.3. Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, the investigators, the Investigational New Drug (IND) and regulatory authorities as appropriate. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and Sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants

- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the Sponsor, IRB and/or FDA.

8.4. Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the Sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third-party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

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

The study participant's contact information will be securely stored at the clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or Sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored by Emmes, the Data Coordinating Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the clinical site and by Emmes research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived.

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

8.5. Risk/Benefit Assessment

8.5.1. Potential Risks

Risk of L9LS: The risk of L9LS is not yet known as this is the first in human study. A similar malaria antibody, CIS43LS, was evaluated as safe and well-tolerated in the VRC 612 study[7].

Investigational monoclonal antibody, L9LS, exhibited scattered membrane binding which localized to the epithelial cells lining the human salivary gland ducts and acini in a preclinical tissue cross-reactivity study. Binding was rare at an antibody concentration of 1.15 µg/ml, and rare to occasional at 11.5 µg/ml. These findings are of unclear clinical significance. Any effect on the salivary glands from L9LS, if present, is expected to be transient due to clearance of the passively transferred antibody over time. Additionally, salivary gland epithelium turns over rapidly which would likewise be expected to decrease any potential complications.

To address these findings, the trial will exclude individuals at an increased risk for salivary gland dysfunction and will prospectively monitor for signs and symptoms that may be indicative of salivary gland abnormality. Subject matter experts in salivary gland disorders at the National Institute of Dental and Craniofacial Research, who are board-certified by the American Board of Oral and Maxillofacial Pathology, have assisted the study team in developing a risk mitigation strategy and have agreed to participate in eligibility or adverse event evaluations as needed by the study team. Evidence of clinically significant salivary gland toxicity will be considered at each dose escalation review and dose escalation would not proceed if clinical toxicity is identified.

Risks of mAb Administration: Administration of mAbs may cause immune reactions such as acute anaphylaxis, serum sickness and the generation of antibodies. However, these reactions are rare and more often associated with mAbs targeted to human proteins or with the use of mouse mAbs that would have a risk of human anti-mouse antibodies [25]. In this regard, because L9LS is targeted to a malaria parasite antigen and is a human mAb, it is expected to have a low risk of such side effects.

Typically, the side effects of mAbs are mild to moderate and may include local reactions at the injection site (including pain, redness, bruising, swelling) and systemic reactions such as fever, chills, rigors, nausea, vomiting, pain, headache, dizziness, shortness of breath, bronchospasm, hypotension, hypertension, pruritus, rash, urticaria, angioedema, diarrhea, tachycardia or chest pain. Clinical use of mAbs that are targeted to cytokines or antigens associated with human cells may be associated with an increased risk of infections [25]; however, this is not expected to be a risk for a mAb targeted to a parasite antigen.

Severe reactions, such as anaphylaxis, angioedema, bronchospasm, hypotension and hypoxia, are infrequent and more often associated with mAbs targeted to human proteins or with non-human mAb, such as a mouse mAb [25]. Most infusion-related events occur within the first 24 hours after initiation of mAb administration.

Published experience with human mAbs directed against cell surface targets on lymphocytes shows that infusion of a mAb may be associated with cytokine release, causing a reaction known as cytokine release syndrome (CRS) [26]. CRS reactions commonly occur within the first few hours of infusion start and with the first mAb infusion received. This is because the cytokine release is associated with lysis of the cells targeted by the mAb and the burden of target cells is

greatest at the time of the first mAb treatment. With licensed therapeutic mAbs, CRS is managed by temporarily stopping the infusion, administering histamine blockers and restarting the infusion at a slower rate [27]. Supportive treatment may also be indicated for some signs and symptoms.

Delayed allergic reactions that include a serum sickness type of reaction characterized by urticaria, fever, lymph node enlargement, and joint pains, typically occur several days after mAb exposure and are more commonly associated with chimeric types of mAbs [25]. In general, and with due consideration of the needs dictated by individual subject symptoms and treating clinician discretion, immediate and delayed reactions to study product would be managed according to the principles of the American Academy of Allergy, Asthma, and Immunology guidelines established in the Drug Allergy: Practice Parameters (2010).

Participation in this study may limit a subject's eligibility for future mAb studies.

Risks of Blood Drawing: Blood drawing may cause pain, bruising, and a feeling of lightheadedness or fainting. Rarely, it may cause infection at the site where blood is taken. In this study, an IV line that can be used for blood collection may be placed in the arm and left in place for several hours on days when there is product administration for frequent PK blood draws. Problems from use of an IV for blood drawing are generally mild and may include pain, bruising, minor swelling or bleeding at the IV site and rarely, infection, vein irritation (phlebitis), or blood clot.

Risks of Mosquito Bites for CHMI: Risks associated with CHMI include local inflammatory reactions, lymphadenitis, persistent local pruritus and larger local reactions involving the whole forearm, allergic reactions to mosquito bites. Another remotely possible risk includes a systemic allergic reaction to the mosquitoes.

Risks of Acquiring Malaria Infection: There is also the possibility of complications of malaria, which are seen during naturally acquired malaria when diagnosis and treatment are delayed and high levels of parasitemia develop. Under the carefully controlled conditions of this study that supports early diagnosis and treatment, the chance of such complications is unlikely and the risk of death from malaria infection is very small. Transient abnormalities, e.g. fever, headache, myalgia, shaking chills, abdominal discomfort, nausea, vomiting, mild anemia, leukopenia, thrombocytopenia, hepatosplenomegaly, hepatic tenderness and fatigue, are expected consequences of malaria. In uncontrolled circumstances, malaria infections can lead to kidney, liver or brain injury (seizures, coma) and death.

Risks of Antimalarial Medication: Additional risks include possible side effects of the antimalarial medication taken (chloroquine) following challenge with chloroquine-sensitive Pf. These side effects include nausea, vomiting, diarrhea, abdominal pain, dizziness, headaches, sleep disturbances, blurred vision, pruritus, skin rash, exacerbation of psoriasis or porphyria, tinnitus, and photosensitivity. Rarely, there may be changes in electrocardiograms and hypotension. Side effects of atovaquone/proguanil (Malarone®) include nausea, vomiting, abdominal pain, anorexia, diarrhea, headache, cough and rarely, anemia, oral ulcerations, insomnia, fever, edema, rash and alopecia. Another remotely possible risk includes a systemic allergic reaction to chloroquine (or Malarone®). The study team will discuss these medications and their possible side effects in detail both as part of the informed consent process, prior to CHMI, and prior to initiation of treatment for diagnosed malaria infections.

Risks of Screening Procedures: The risks of screening procedures can be found in the VRC-sponsored screening protocol VRC 500 (NIH 11-I-0164, NCT01375530) used for all VRC IND studies conducted at the NIH Clinical Center.

8.5.2. Potential Benefits

Study subjects will not receive direct health benefit from study participation. Others may benefit from knowledge gained in this study that may aid in the development of malaria prevention.

8.5.3. Assessment of Potential Risks and Benefits

This research study will be conducted in compliance with the protocol, GCP guidance, and all applicable regulatory requirements.

The plan for reduction of known and unknown risks to participants includes appropriate training of study personnel; education of study subjects for participation in care throughout the study; monitoring of study subject's health status and experiences; withdrawal from study procedures upon evidence of difficulty, contraindication, or a significant adverse event; and referral for treatment, counseling or other necessary follow-up. The VRC CTP Risk Management Plan guides the reduction and mitigation strategies applied to the known and unknown risks associated with study participation and trial management/operations.

As study subjects will not receive direct health benefit from study participation or product administration, no alternative procedures are planned. The alternative course of action is to choose not to participate.

8.6. Plan for Use and Storage of Biological Samples

The plan for use and storage of biological samples from this protocol is 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, parasitology and immunogenicity evaluations, exploratory laboratory evaluations related to malaria, exploratory laboratory evaluations related to mAb, vaccine or infectious disease research in general and for research assay validation.

Stored samples may also be used later for exploratory genetic factors that may influence the immune response. No specific results will be provided to participants or their health care providers because we will not be investigating genetic analyses that have known medical diagnoses (e.g. Huntington's disease) or other medically actionable genetic information.

8.6.2. Storage and Tracking of Blood Samples and Other Specimens

All research samples use coded labels that only the VRC VEC can link to the subject. Samples are stored at VIP or VRC laboratories in Building 40, Bethesda, MD, which are both 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 with non-NIH investigators and any clinical information shared about those samples would similarly require prior IRB approval. The research use of stored, unlinked or unidentified samples will 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 remain in the VIP facility or VRC laboratories or, after IRB approval, will be transferred to another repository. Regulatory oversight of the stored samples and data may be transferred to a stored samples protocol as part of the IRB approved termination plan. Data will be archived by the VRC in compliance with requirements for retention of research records, or after IRB and study 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) will be reported to the IRB. The Protocol Chair or PI will also notify the IRB if the decision is made to destroy the remaining samples.

Neither participation nor refusal to participate will have an effect, either beneficial or adverse, on the participant's employment or work situation. The NIH information sheet regarding NIH employee research participation will be distributed to all potential subjects who are NIH employees. The employee subject's privacy and confidentiality will be preserved in accordance with applicable policies at the study site. For any employee subjects, consent will be obtained by an individual who is independent of the employee's team. At NIH, if the individual obtaining consent is a co-worker to the subject, independent monitoring of the consent process will be included through the Bioethics Consultation Service. Protocol study staff will be trained on obtaining potentially sensitive and private information from co-workers or subordinates.

8.7. Safety Oversight

Close cooperation between the designated members of the Protocol Team will occur to evaluate and respond to individual AEs in a timely manner. The VRC clinic designated Safety Officer (SO) for the day conducts a daily safety review of clinical data per VRC Standard Operating Procedures. A Protocol Safety Review Team (PSRT) comprised of the Principal Investigator (PI), Associate Investigators, Study Coordinator, Protocol Specialists, other study clinicians, and the IND MO, will review the summary study safety data reports per the protocol-defined frequency. In addition, an Independent Safety Monitor (ISM), who is not associated with the VRC will provide safety oversight.

The designated ISM will receive safety reports that contains a line listing of all adverse events that occurred to date. The ISM will meet with the PSRT during the weekly protocol safety meeting to clarify, discuss, and provide an impression of the safety data acquired to date. Meetings and safety report distribution will transition to a monthly schedule beginning 4 weeks after the last product administration to the final subject. Weekly safety meetings will resume for

4 weeks after CHMI. All adverse events, including those that are expected, will be contained in the weekly safety reports and will be available for independent review by the ISM. The overall findings and recommendations that result from the safety meetings will be documented in a protocol interim safety review form that will document adverse events that have occurred, including specifically any that may trigger pause criteria, serious adverse events, and comments from the group related to the adverse events. Attendance by the PI or designee, Medical Officer and/or ISM is documented on the form and officially signed by the PI or designee. The signed interim safety review form will be sent to the ISM and the PSRT so that all are aware of any emerging safety signals even if unable to attend a PSRT meeting.

9. ADMINISTRATIVE AND OPERATIONAL OBLIGATIONS

9.1. Protocol Amendments and Study Termination

Protocol amendments must be made only with prior approval of the IND Sponsor and with agreement from the PI and MO. All study amendments will be submitted to the IRB for approval.

The IND Sponsor, the IRB, OHRP, the PI, Protocol Chairs, and/or the FDA reserve the right to terminate the study. The PI will notify the IRB in writing of the study's completion or early termination.

9.2. Study Documentation and Storage

The PI will delegate the study responsibilities to the study team, and a list of appropriately qualified persons to whom trial duties have been delegated will be maintained.

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, and correspondence. Long-term storage of source documents may be in the form of electronic files.

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

- Subject files containing completed informed consent forms, and supporting copies of source documentation.
- Study files containing the protocol with all amendments, IBs, copies of all correspondence with the IRB.

In addition, all original source documentation must be maintained and be readily available.

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 (21 CFR 312.62). 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 FDA is notified. The HHS protection of human subjects' regulations require that institutions retain records of IRB/EC activities and documentation of informed consent of subjects for at least 3 years after study completion (45 CFR 46).

No study document should be destroyed without prior written agreement between the VRC and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, they must notify the VRC in writing of the new responsible person and/or the new location.

9.3. Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the

conduct of the trial is in compliance with the currently approved protocol/amendment(s), with ICH GCP, and with applicable regulatory requirement(s).

Monitoring for this study will be performed by a designated contract research organization (CRO). Details of clinical site monitoring are documented in a Clinical Monitoring Plan. The Clinical Monitoring Plan describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

9.4. Data Collection and Sharing

9.4.1. Data Collection

Clinical research data will be collected in a secure electronic web-based clinical data management system (CDMS) through a CRO, Emmes (Rockville, MD). Extracted, anonymized data will be sent to the PSRT for safety review and to the Protocol Statistician for statistical analysis.

9.4.2. Source Documents

The site will maintain appropriate medical and research records for this trial, in compliance with ICH E6(R2) GCP, applicable regulations, 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.

9.4.3. Data Sharing

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 one year of the primary completion date.

9.5. Quality Assurance and Quality Control

The clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. The VEC's Quality Management Plan will be used to perform quality management for this trial.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site for clarification/resolution.

The monitors will verify that the clinical trial is conducted, and data are generated, and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

The site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

9.6. Language

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

9.7. Research-Related Injuries

9.7.1. NIH

The NIH Clinical Center will provide short-term medical care for any injury resulting from participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the NIH, the NIH Clinical Center, or the Federal Government. However, subjects have the right to pursue legal remedy if they believe that their injury justifies such action.

9.7.2. WRAIR

If subjects are injured because of participation in this research during the CHMI and they are a DOD healthcare beneficiary (e.g., active duty in the military, military spouse or dependent, retiree), they are entitled to medical care for their injury within the DOD healthcare system, as long as they remain a DOD healthcare beneficiary.

If subjects are injured because of participation in this research during the CHMI and they are not a DOD healthcare beneficiary, they are entitled to medical care for their injury at a DOD hospital or clinic, but such care for the injury at DOD hospitals or clinics may be time-limited, and the subject's insurance may be billed. It cannot be determined in advance which DOD hospital or clinic will provide care. If subjects obtain care for research-related injuries outside of a DOD hospital or clinic, they or their insurance will be responsible for medical expenses.

For DOD healthcare beneficiaries and non-DOD healthcare beneficiaries: Transportation to and from hospitals or clinics will not be provided. No reimbursement is available if subjects incur medical expenses to treat research-related injuries. No compensation is available for research-related injuries. Subjects are not waiving any legal rights. If subjects believe they have sustained a research-related injury, they may contact the PI. If subjects have any questions, they can contact the PI.

9.8. WRAIR Facility and CHMI Management

The VRC, NIAID, NIH is the coordinating center as well as the only clinical site for this protocol. Dr. Richard Wu, VRC, NIAID, NIH, is the site PI overseeing the management and monitoring of the protocol conduct overall.

Investigators from WRAIR, the facility that will be administering the CHMI, will have limited interaction with study subjects during the administration of the CHMI. Certain immediate pre- and post-CHMI assessments of subjects will take place in the CHMI facility with some

participation by CHMI facility personnel and NIH staff. All other post-CHMI clinical visits for subjects will take place at the NIH clinical site.

A Reliance Agreement will be established with the collaborating CHMI facility such that the NIH IRB is the IRB of Record for the conduct of the VRC 614 protocol. Referring to Section 5 of the VRC 614 protocol, any Serious Adverse Events, Unanticipated Problems or Protocol Deviation which are reportable to the NIH IRB which are in relation to the conduct of the CHMI will also be communicated to the collaborating CHMI facility within the same reporting period specified in the protocol.

9.8.1. Roles and Responsibilities for the CHMI

The PI will delegate responsibility for overseeing the administration of the CHMI at the collaborating CHMI facility (i.e., application of and assessment of the mosquito bites) to designated Associate Investigators from those facilities. Follow-up and medical care of the study subjects after the CHMI is administered remains the responsibility of the site PI and the designated personnel at the clinical site.

The Authorized Representative from the CHMI facility may review research records related to the CHMI conducted at their own facility.

The roles and responsibilities for this collaborating institution and facility personnel for the conduct of CHMI as described above are delineated in the corresponding VRC 614 Study Personnel Page.

9.8.2. WRAIR Protocol Review and Reporting Requirements

Initial Protocol Review

WRAIR will defer their IRB review to the NIH IRB once a reliance agreement is in place. WRAIR Human Subjects Protection Branch (HSPB) will still perform an administrative review of the protocol to ensure that the WRAIR reporting requirements are met. WRAIR Commander Approval Authorization will be issued once the NIH IRB approval has been submitted to the WRAIR HSPB and the administrative WRAIR comments have been adequately addressed. Headquarters level review will be conducted as appropriate.

Protocol Modifications/Amendments

All amendments/modifications to the protocol and supporting documents (informed consent, recruitment materials, etc.) must be reviewed by the WRAIR HSPB and a WRAIR Commander Authorization Approval issued prior to WRAIR participation on the amended/modified protocol.

Continuing Reviews and Closeout Report

The WRAIR Point of Contact will be responsible for preparing and submitting continuing review reports as per UWS-HP-618.03 and a closeout report as per WRAIR Policy #30. The WRAIR HSPB will review and acknowledge the reports in order for WRAIR personnel to continue their participation on the study. Once all study activities have been completed, to include data analysis, a closeout report will need to be submitted to the WRAIR HSPB to close the study.

The following reporting requirements apply:

Unanticipated Problems Involving Risks to Subjects or Others

Unanticipated problems, as defined in Section 5.5.1, should be promptly reported (48 hours) by telephone, email, or fax to the WRAIR HSPB. A complete written report should follow the initial notification within 10 working days. All unanticipated problems occurring within the reporting period should also be summarized in the continuing review reports submitted to the WRAIR HSPB (contact information is below at end of section).

Serious Adverse Events

All related SAEs and deaths, as defined in Section 5.2, should be reported to the WRAIR HSPB within 48 hours by telephone, email, or fax. A complete written report should follow the initial notification within 10 working days. All SAEs occurring within the reporting period should also be summarized in the continuing review reports submitted to the WRAIR HSPB.

Protocol Deviations

All major protocol deviations that adversely affect the safety or rights of a subject or scientific integrity of the study, as defined in Section 5.5.3, will be reported to the WRAIR HSPB within 48 hours and a written report should be submitted within 10 working days. All protocol deviations occurring within the reporting period should be summarized in the continuing review reports that are submitted to the WRAIR HSPB.

Pending Inspections/Issuance of Reports

The knowledge of any pending compliance inspection/visit by the FDA, Office for Human Research Protections (Department of Health and Human Services), or other government agency concerning clinical investigation or research, the issuance of Inspection Reports, FDA Form 483, warning letters, or actions taken by any regulatory agency including legal or medical actions and any instances of serious or continuing noncompliance with the regulations or requirements will be reported immediately to the WRAIR HSPB.

WRAIR HSPB Contact Information

Director, Human Subjects Protection Branch
503 Robert Grant Avenue
Silver Spring, MD 20910
Telephone: 301-319-9940 Fax: 301-319-9961
E-mail: usarmy.detrick.medcom-wrair.mbx.hspb@mail.mil

10. REFERENCES

1. Sachs, J. and P. Malaney, *The economic and social burden of malaria.* Nature, 2002. **415**(6872): p. 680-5.
2. *Roll Back Malaria*. Global Malaria Action Plan 2008 2008; Available from: http://www.rbm.who.int/keyfacts.html.
3. Breman, J.G., *Eradicating malaria.* Sci Prog, 2009. **92**(Pt 1): p. 1-38.
4. Rts, S.C.T.P., *Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial.* Lancet, 2015. **386**(9988): p. 31-45.
5. Mahmoudi, S. and H. Keshavarz, *Efficacy of phase 3 trial of RTS, S/AS01 malaria vaccine: The need for an alternative development plan.* Hum Vaccin Immunother, 2017. **13**(9): p. 2098-2101.
6. Wang, L.T., et al., *A Potent Anti-Malarial Human Monoclonal Antibody Targets Circumsporozoite Protein Minor Repeats and Neutralizes Sporozoites in the Liver.* Immunity, 2020. **53**(4): p. 733-744 e8.
7. Gaudinski, M.R., et al., *A Monoclonal Antibody for Malaria Prevention.* New England Journal of Medicine, 2021. **385**(9): p. 803-814.
8. Gaudinski, M.R., et al., *Safety and pharmacokinetics of the Fc-modified HIV-1 human monoclonal antibody VRC01LS: A Phase 1 open-label clinical trial in healthy adults.* PLoS Med, 2018. **15**(1): p. e1002493.
9. Ledgerwood, J.E., et al., *Safety, pharmacokinetics and neutralization of the broadly neutralizing HIV-1 human monoclonal antibody VRC01 in healthy adults.* Clin Exp Immunol, 2015. **182**(3): p. 289-301.
10. Gaudinski, M.R., et al., *Safety, tolerability, pharmacokinetics, and immunogenicity of the therapeutic monoclonal antibody mAb114 targeting Ebola virus glycoprotein (VRC 608): an open-label phase 1 study.* Lancet, 2019. **393**(10174): p. 889-898.
11. Gaudinski, M.R., et al., *Safety and pharmacokinetics of broadly neutralising human monoclonal antibody VRC07-523LS in healthy adults: a phase 1 dose-escalation clinical trial.* Lancet HIV, 2019. **6**(10): p. e667-e679.
12. Chulay, J.D., et al., *Malaria transmitted to humans by mosquitoes infected from cultured Plasmodium falciparum.* Am J Trop Med Hyg, 1986. **35**(1): p. 66-8.
13. Seder, R.A., et al., *Protection against malaria by intravenous immunization with a nonreplicating sporozoite vaccine.* Science, 2013. **341**(6152): p. 1359-65.
14. Lyke, K.E., et al., *Attenuated PfSPZ Vaccine induces strain-transcending T cells and durable protection against heterologous controlled human malaria infection.* Proc Natl Acad Sci U S A, 2017. **114**(10): p. 2711-2716.
15. Roestenberg, M., et al., *Experimental infection of human volunteers.* Lancet Infect Dis, 2018. **18**(10): p. e312-e322.
16. Nieman, A.E., et al., *Cardiac complication after experimental human malaria infection: a case report.* Malar J, 2009. **8**: p. 277.
17. Moorthy, V.S., et al., *Report of a consultation on the optimization of clinical challenge trials for evaluation of candidate blood stage malaria vaccines, 18-19 March 2009, Bethesda, MD, USA.* Vaccine, 2009. **27**(42): p. 5719-25.
18. van Meer, M.P., et al., *Idiopathic acute myocarditis during treatment for controlled human malaria infection: a case report.* Malar J, 2014. **13**: p. 38.

19. Deye, G.A., et al., *Prolonged protection provided by a single dose of atovaquone-proguanil for the chemoprophylaxis of Plasmodium falciparum malaria in a human challenge model.* Clin Infect Dis, 2012. **54**(2): p. 232-9.
20. Stanisic, D.I., et al., *Development of cultured Plasmodium falciparum blood-stage malaria cell banks for early phase in vivo clinical trial assessment of anti-malaria drugs and vaccines.* Malar J, 2015. **14**: p. 143.
21. Mejia, R., et al., *Peripheral blood stem cell transplant-related Plasmodium falciparum infection in a patient with sickle cell disease.* Transfusion, 2012. **52**(12): p. 2677-82.
22. Shokoples, S.E., et al., *Multiplexed real-time PCR assay for discrimination of Plasmodium species with improved sensitivity for mixed infections.* J Clin Microbiol, 2009. **47**(4): p. 975-80.
23. Gaziano, T.A., et al., *Laboratory-based versus non-laboratory-based method for assessment of cardiovascular disease risk: the NHANES I Follow-up Study cohort.* Lancet, 2008. **371**(9616): p. 923-31.
24. Ammon, H., *Drugs and the Pharmaceutical Sciences, Vol. 1: PHARMACOKINETICS, von M. Gibaldi und D. Perrier, 360 S., Preis $. 19,50, Marcel Dekker Verlag, New York 1975.* Archiv der Pharmazie, 1976. **309**.
25. Hansel, T.T., et al., *The safety and side effects of monoclonal antibodies.* Nat Rev Drug Discov, 2010. **9**(4): p. 325-38.
26. Bugelski, P.J., et al., *Monoclonal antibody-induced cytokine-release syndrome.* Expert Rev Clin Immunol, 2009. **5**(5): p. 499-521.
27. Vogel, W.H., *Infusion reactions: diagnosis, assessment, and management.* Clin J Oncol Nurs, 2010. **14**(2): p. E10-21.

APPENDIX I: SCHEDULE OF EVALUATIONS

Schedule of Evaluations: IV Groups (Groups 1, 2, 4)																			
Visit Number		01	[1] 01R	[1] 02	02A	02B	02C	02D	03	04	06	07	08	09	10	11	12	13	14
Time After Infusion				Pre	EOI	1hr	3h	6h	24hr	48hr	Wk1	Wk2	Wk3	Wk4	Wk8	Wk12	Wk16	Wk20	Wk24
Day of Study		-56 to -1	-28 to 0	D0	D0	D0	D0	D0	D1	D2	D7	D14	D21	D28	D56	D84	D112	D140	D168
Study Procedures	**Tube**	**Screen**	**Enroll**	**Day of infusion**															
VRC 500 Screening Consent		X																	
VRC 614 Informed Consent, AoU			X																
[2] Physical Exam		X	X	X	X				X	X	X	X	X	X	X	X	X	X	X
[3] Medical History		X	X	X					X	X	X	X	X	X	X	X	X	X	X
EKG		X																	
Concomitant Medications		X	X	X					X	X	X	X	X	X	X	X	X	X	X
Product Administration				**X**															
Begin 7-day Diary Card				X															
[4] Pregnancy Prevention Counseling		X	X	X								X					X		X
Clinical Evaluations																			
[4] Pregnancy Test (urine or serum)		X	X	X								X					X		X
CBC with differential	EDTA	3		3					3		3	3		3		3			
ALT, creatinine	GLT	X		X					4		4	4		4		4			
[5] CMP	GLT	4		4															
HIV Ag/Ab Combo	EDTA	3																	
Sickle Cell Test	EDTA	3																	
Parasitemia Evaluation (PCR)	EDTA	3																	
Research Samples																			
[6] PK	SST			4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
PBMC	EDTA	20										40							
Serum	SST	8		16†						8	8†	8	8	8†	8	8†	8	8	8†
Daily Volume (mL)		**44**	**0**	**27**	**4**	**4**	**4**	**4**	**11**	**12**	**19**	**59**	**12**	**19**	**12**	**19**	**12**	**12**	**12**
Cumulative Volume (mL)		**44**	**44**	**71**	**75**	**79**	**83**	**87**	**98**	**110**	**129**	**188**	**200**	**219**	**231**	**250**	**262**	**274**	**286**

Visit windows: Schedule Visits 02A–14 with respect to Visit 02. Visit 02A (within 10 min of EOI); Visits 02B, 02C (±10 min); Visit 02D (-2 hrs); Visits 03, 04 (±6 hrs); Visits 06, 07, 08, 09 (±2 days); Visits 10, 11, 12, 13, 14 (±7 days). Visit 05 is not applicable to this schedule.

Footnotes (continue to next page):

[1] Visit 01R is the day of enrollment and may be done on the same day as Day 0. V02/Day 0 is day of product administration and preferably scheduled within 14 days after enrollment at Visit 01R but may be scheduled up to 28 days after Visit 01R.

[2] Screening includes physical exam, vital signs (blood pressure (BP), temperature, pulse, respiratory rate (RR)), height, weight. Day 0 includes vital signs and weight (for ordering study product dose). At other visits, perform a targeted exam if medically indicated, otherwise only vital signs are required.

[3] Perform full medical history at screening. At other visits, perform interim medical history

[4] Pregnancy test results must be negative for women of reproductive potential before product administration. Complete Pregnancy Prevention Counseling Form when pregnancy test is done.

[5] CMP includes sodium, potassium, chloride, total CO_2, creatinine, glucose, urea nitrogen, albumin, alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, total bilirubin, calcium, total protein

[6] PK blood draws, defined by time after an infusion, are relative to the exact time of the end of infusion (EOI). Record the exact start / end times of product administration and of blood draw to ensure accurate PK analysis.

[†] Anti-drug antibodies (ADA) assessed from serum samples at timepoints as indicated.

Schedule of Evaluations: SC Group (Group 3)																	
Visit Number		01	[1] 01R	[1] 02	02A	03	04	05	06	07	08	09	10	11	12	13	14
Time after Infusion				Pre	EOI	24hr	48hr	72hr	Wk1	Wk2	Wk3	Wk4	Wk8	Wk12	Wk16	Wk20	Wk24
Study Day		-56 to -1	-28 to 0	D0	D0	D1	D2	D3	D7	D14	D21	D28	D56	D84	D112	D140	D168
Study Procedures	**Tube**	**Screen**	**Enroll**	**Day of injection**													
VRC 500 Screening Consent		X															
VRC 614 Informed Consent, AoU			X														
[2] Physical Exam		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[3] Medical History		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
EKG		X															
Concomitant Medications		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Product Administration				**X**													
Begin 7-day Diary Card				X													
[4] Pregnancy Prevention Counseling		X	X	X						X					X		X
Clinical Evaluations																	
[4] Pregnancy Test (urine or serum)		X	X	X						X					X		X
CBC with differential	EDTA	3		3		3			3	3		3		3			
ALT, creatinine	GLT	X		X		4			4	4		4		4			
[5] CMP	GLT	4		4													
HIV Ag/Ab Combo	EDTA	3															
Sickle Cell Test	EDTA	3															
Parasitemia Evaluation (PCR)	EDTA	3															
Research Samples																	
[6] PK	SST			4		4	4	4	4	4	4	4	4	4	4	4	4
PBMC	EDTA	20								40							
Serum	SST	8		16†			8	8	8†	8	8	8†	8	8†	8	8	8†
Daily Volume (mL)		**44**	**0**	**27**	**0**	**11**	**12**	**12**	**19**	**59**	**12**	**19**	**12**	**19**	**12**	**12**	**12**
Cumulative Volume (mL)		**44**	**44**	**71**	**71**	**82**	**94**	**106**	**125**	**184**	**196**	**215**	**227**	**246**	**258**	**270**	**28**

Visit windows: Schedule Visits 02A –14 with respect to Visit 02. Visit 02A (within 10 min of EOI); Visits 03, 04, 05 (±6 hrs); Visits 06, 07, 08, 09 (±2 days); Visits 10, 11, 12, 13, 14 (±7 days).

Footnotes (continue to next page):

[1] Visit 01R is the day of enrollment and may be done on the same day as Day 0. V02/Day 0 is day of product administration and preferably scheduled within 14 days after enrollment at Visit 01R but may be scheduled up to 28 days after Visit 01R.

[2] Screening includes physical exam, vital signs (BP, temperature, pulse, RR), height, weight. Day 0 includes vital signs and weight (for ordering study product dose). At other visits, perform a targeted exam if medically indicated, otherwise only vital signs are required.

[3] Perform full medical history at screening. At other visits, perform interim medical history.

[4] Pregnancy test results must be negative for women of reproductive potential before product administration. Complete Pregnancy Prevention Counseling Form when pregnancy test is done.

[5] CMP includes sodium, potassium, chloride, total CO_2, creatinine, glucose, urea nitrogen, albumin, alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, total bilirubin, calcium, total protein.

[6] PK blood draws, defined by time after infusion, are relative to the exact time of the end of infusion (EOI). Record exact start / end times of product administration and of blood draw to ensure accurate analysis.

[†] ADA assessed from serum samples at timepoints as indicated.

Schedule of Evaluations: IM Group (Group 6)																	
Visit Number		01	[1] 01R	[1] 02	02A	03	04	05	06	07	08	09	10	11	12	13	14
Time after Infusion				Pre	EOI	24hr	48hr	72hr	Wk1	Wk2	Wk3	Wk4	Wk8	Wk12	Wk16	Wk20	Wk24
Study Day		-56 to -1	-28 to 0	D0	D0	D1	D2	D3	D7	D14	D21	D28	D56	D84	D112	D140	D168
Study Procedures	**Tube**	**Screen**	**Enroll**	**Day of injection**													
VRC 500 Screening Consent		X															
VRC 614 Informed Consent, AoU			X														
[2] Physical Exam		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[3] Medical History		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Product Administration				**X**													
Begin 7-day Diary Card				X													
[4] Pregnancy Prevention Counseling		X	X	X						X					X		X
Clinical Evaluations																	
[4] Pregnancy Test (urine or serum)		X	X	X						X					X		X
CBC with differential	EDTA	3		3		3			3	3		3		3			
ALT, creatinine	GLT	X		X		4			4	4		4		4			
[5] CMP	GLT	4		4													
HIV Ag/Ab Combo	EDTA	3															
Research Samples																	
[6] PK	SST			4		4	4	4	4	4	4	4	4	4	4	4	4
PBMC	EDTA	20								40							
Serum	SST	8		16†			8	8	8†	8	8	8†	8	8†	8	8	8†
Daily Volume (mL)		**44**	**0**	**27**	**0**	**11**	**12**	**12**	**19**	**59**	**12**	**19**	**12**	**19**	**12**	**12**	**12**
Cumulative Volume (mL)		**44**	**44**	**71**	**71**	**82**	**94**	**106**	**125**	**184**	**196**	**215**	**227**	**246**	**258**	**270**	**28**

Visit windows: Schedule Visits 02A –14 with respect to Visit 02. Visit 02A (within 10 min of EOI); Visits 03, 04, 05 (±6 hrs); Visits 06, 07, 08, 09 (±2 days); Visits 10, 11, 12, 13, 14 (±7 days).

Footnotes (continue to next page):

[1] Visit 01R is the day of enrollment and may be done on the same day as Day 0. V02/Day 0 is day of product administration and preferably scheduled within 14 days after enrollment at Visit 01R but may be scheduled up to 28 days after Visit 01R.

[2] Screening includes physical exam, vital signs (BP, temperature, pulse, RR), height, weight. Day 0 includes vital signs and weight (for ordering study product dose). At other visits, perform a targeted exam if medically indicated, otherwise only vital signs are required.

[3] Perform full medical history at screening. At other visits, perform interim medical history.

[4] Pregnancy test results must be negative for women of reproductive potential before product administration. Complete Pregnancy Prevention Counseling Form when pregnancy test is done.

[5] CMP includes sodium, potassium, chloride, total CO_2, creatinine, glucose, urea nitrogen, albumin, alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, total bilirubin, calcium, total protein.

[6] PK blood draws, defined by time after infusion, are relative to the exact time of the end of infusion (EOI). Record exact start / end times of product administration and of blood draw to ensure accurate analysis.

[†] ADA assessed from serum samples at timepoints as indicated

Schedule of Evaluations: CHMI for Groups 1-4													
Visit Number		C01	C02	[1] C02A	[1] C02B	C03	C04	C05	C06	C07	C08	C09	C10
Time after CHMI				24hr	72hr	Wk1	Wk1	Wk1	Wk1	Wk1	Wk1	Wk1	Wk2
CHMI Day		-1	D0	D1	D3	D7	D8	D9	D10	D11	D12	D13	D14
Study Procedures	Tube		**CHMI**			**Parasitemia Check** (daily checks until treatment criteria met)							
[2] Physical Exam, Vital Signs		X	X			X	X	X	X	X	X	X	X
Interim Medical History		X	X			X	X	X	X	X	X	X	X
CHMI			**X**										
Phone Contact				X	X								
Pregnancy Prevention Counseling		X											
Clinical Evaluations													
[3] Pregnancy Test (urine or serum)		X											
CBC with differential	EDTA	3				3							
ALT, creatinine	GLT	4											
[4] Parasitemia Evaluation (PCR)	EDTA					3	3	[3]	[3]	[3]	[3]	[3]	[3]
Research Samples													
PK	SST	4				4							4
PBMC	EDTA					40							*60
Serum	SST					16[†]							*16
Daily Volume (mL)		**11**	**0**	**0**	**0**	**66**	**3**	**3**	**3**	**3**	**3**	**3**	**83**
Cumulative Volume (mL)		**11**	**11**	**11**	**11**	**77**	**80**	**83**	**86**	**89**	**92**	**95**	**178**

[1] After CHMI, schedule Visit C02A on Day 1 or 2, Visit C02B on Day 3 or 4.

[2] Perform a targeted physical exam if medically indicated, otherwise only vital signs (BP, temperature, pulse, RR) are required.

[3] Pregnancy test results must be negative for women of reproductive potential within 2 days prior to CHMI. Complete a Pregnancy Prevention Counseling Form when pregnancy test is done.

[4] Parasitemia evaluations should continue daily until a subject has one positive PCR or blood smear; brackets [3] indicate optional draw as needed. A positive result prior to Day 21 is required for initiation of antimalarial directly observed therapy (DOT).

* Research blood will be drawn at 14 days post-CHMI (Visit C10) from all subjects.

[†] ADA assessed from serum samples at timepoints as indicated.

Schedule of Evaluations: CHMI for Groups 1-4 (continued)									
[1] Visit Number		C11	C12	C13	[1] C14	C15	C16	C17	[2] C18
Time after CHMI		Wk2	Wk2	Wk2	Wk3	Wk3	Wk3	Wk4	Wk7
CHMI Day		D15	D16	D17	D21	D22	D23	D28	D49
Study Procedures	**Tube**	**Parasitemia Check** (daily until treatment criteria met)							
[3] Physical Exam, Vital Signs		X	X	X	X	X	X		[X]
Interim Medical History		X	X	X	X	X	X		[X]
Phone Contact								X	[X]
Clinical Evaluations									
CBC with differential	EDTA				*3		*3		[3]
ALT, creatinine	GLT				*4		*4		[4]
[4] Parasitemia Evaluation (PCR)	EDTA	[3]	[3]	[3]	[3]				[3]
Anti-Malarial Treatment					[X]	[X]	[X]		
Research Samples									
PK	SST				4				[4]
PBMC	EDTA								[60]
Serum	SST				8†				[16]
Daily Volume (mL)		**3**	**3**	**3**	**22**	**0**	**7**	**0**	**90**
Cumulative Volume (mL)		**181**	**184**	**187**	**209**	**209**	**216**	**216**	**306**

[1] Visit C14 is only required for CHMI participants not previously diagnosed with malaria parasitemia to rule out a delayed case. At Visit C14 (Day 21), any subject who has not already started antimalarial treatment will be given definitive DOT. Subjects must return for DOT for 2 more days after initiation. Brackets [X] indicate optional as needed per subject treatment status.

[2] Visit C18 is only required for subjects who had a positive PCR or blood smear to document test of cure. It is scheduled to occur 26±5 days after DOT completion and is shown at Day 49 for convenience. Visit C18 may be completed via phone for subjects who remain malaria negative, brackets [X] indicate optional as needed per subject infection status.

[3] Perform a targeted physical exam if medically indicated, otherwise only vital signs (BP, temperature, pulse, RR) are required.

[4] Parasitemia evaluations should continue daily until a subject has one positive PCR or blood smear; brackets [3] indicate optional draw as needed. A positive result prior to Day 21 is required for initiation of antimalarial DOT. Otherwise, initiate DOT at C14.

* Blood for CBC, ALT, and creatinine will be drawn at onset of DOT and about 2 days later; shown at visits C14 and C16 to account for blood draw. Parasitemia evaluations are not performed during treatment through to test of cure.

† ADA assessed from serum samples at timepoints as indicated.

Schedule of Evaluations: CHMI for Group 5																
Visit Number		01	01R	C01	C02	[1] C02A	[1] C02B	C03	C04	C05	C06	C07	C08	C09	C10
Time after CHMI						24hr	72hr	Wk1	Wk1	Wk1	Wk1	Wk1	Wk1	Wk1	Wk2
CHMI Day		-56 to -1	-56 to -1	-1	D0	D1	D3	D7	D8	D9	D10	D11	D12	D13	D14
Study Procedures	Tube				**CHMI**			**Parasitemia Check** (daily checks until treatment criteria met)							
VRC 500 Screening Consent		X													
VRC 614 Informed Consent, AoU			X												
[2] Physical Exam, Vital Signs		X	X	X	X			X	X	X	X	X	X	X	X
[3] Medical History		X	X	X	X			X	X	X	X	X	X	X	X
EKG		X													
Concomitant Medications		X		X											
CHMI					**X**										
Phone Contact						X	X								
[4] Pregnancy Prevention Counseling		X	X	X											
Clinical Evaluations															
[4] Pregnancy Test (urine or serum)		X	X	X											
CBC with differential	EDTA	3		3				3							
ALT, creatinine	GLT	X		4											
[5] CMP	GLT	4													
HIV Ag/Ab Combo	EDTA	3													
Sickle Cell Test	EDTA	3													
[6] Parasitemia Evaluation (PCR)	EDTA	3						3	3	[3]	[3]	[3]	[3]	[3]	[3]
Research Samples															
PBMC	EDTA	20						20							*20
Serum	SST	8						8							*8
Daily Volume (mL)		**44**	**0**	**7**	**0**	**0**	**0**	**34**	**3**	**3**	**3**	**3**	**3**	**3**	**31**
Cumulative Volume (mL)		**44**	**44**	**51**	**51**	**51**	**51**	**85**	**88**	**91**	**94**	**97**	**100**	**103**	**134**

Footnotes (continue to next page):

[1] After CHMI, schedule Visit C02A on Day 1 or 2, Visit C02B on Day 3 or 4.

[2] Screening includes physical exam, vital signs (BP, temperature, pulse, RR), height, weight. Day 0 includes vital signs and weight (for ordering study product dose). At other visits, perform a targeted exam if medically indicated, otherwise only vital signs are required.

[3] Perform full medical history at screening. At other visits, perform interim medical history.

[4] Pregnancy test results must be negative for women of reproductive potential within 2 days prior to CHMI. Complete a Pregnancy Prevention Counseling Form when pregnancy test is done.

[5] CMP includes sodium, potassium, chloride, total CO2, creatinine, glucose, urea nitrogen, albumin, alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, total bilirubin, calcium, total protein.

[6] Parasitemia evaluations should continue daily until a subject has one positive PCR or blood smear; brackets [3] indicate optional draw as needed. A positive result prior to Day 21 is required for initiation of antimalarial directly observed therapy (DOT).

* Research blood will be drawn at 14 days post-CHMI (Visit C10) from all subjects.

Schedule of Evaluations: CHMI for Group 5 (continued)									
[1] Visit Number		C11	C12	C13	[1] C14	C15	C16	C17	[2] C18
Time after CHMI		Wk2	Wk2	Wk2	Wk3	Wk3	Wk3	Wk4	Wk7
CHMI Day		D15	D16	D17	D21	D22	D23	D28	D49
Study Procedures	**Tube**	**Parasitemia Check** (daily until treatment criteria met)							
[3] Physical Exam, Vital Signs		X	X	X	X	X	X		[X]
Interim Medical History		X	X	X	X	X	X		[X]
Phone Contact								X	[X]
Clinical Evaluations									
CBC with differential	EDTA				*3		*3		[3]
ALT, creatinine	GLT				*4		*4		[4]
[4] Parasitemia Evaluation (PCR)	EDTA	[3]	[3]	[3]	[3]				[3]
Anti-Malarial Treatment					[X]	[X]	[X]		
Research Samples									
PBMC	EDTA								[20]
Serum	SST								[8]
Daily Volume (mL)		**3**	**3**	**3**	**10**	**0**	**7**	**0**	**38**
Cumulative Volume (mL)		**137**	**140**	**143**	**153**	**153**	**160**	**160**	**198**

[1] Visit C14 is only required for CHMI participants not previously diagnosed with malaria parasitemia to rule out a delayed case. At Visit C14 (Day 21), any subject who has not already started antimalarial treatment will be given definitive DOT. Subjects must return for DOT for 2 more days after initiation. Brackets [X] indicate optional as needed per subject treatment status.

[2] Visit C18 is only required for subjects who had a positive PCR or blood smear to document test of cure. It is scheduled to occur 26±5 days after DOT completion and is shown at Day 49 for convenience. Visit C18 may be completed via phone for subjects who remain malaria negative, brackets [X] indicate optional as needed per subject infection status.

[3] Perform a targeted physical exam if medically indicated, otherwise only vital signs (BP, temperature, pulse, RR) are required.

[4] Parasitemia evaluations should continue daily until a subject has one positive PCR or blood smear; brackets [3] indicate optional draw as needed. A positive result prior to Day 21 is required for initiation of antimalarial DOT. Otherwise, initiate DOT at C14.

* Blood for CBC, ALT, and creatinine will be drawn at onset of DOT and about 2 days later; shown at visits C14 and C16 to account for blood draw. Parasitemia evaluations are not performed during treatment through to test of cure.

APPENDIX II: ASSESSMENT OF AE RELATIONSHIP AND SEVERITY GRADING

Assessment of Relationship of an Adverse Event

The relationship between an AE and the study product or CHMI will be assessed by the investigator on the basis of clinical judgment and the definitions below.

- **Definitely Related**: The AE and administration of study product and/or CHMI are related in time, and a direct association can be demonstrated.
- **Probably Related**: The AE and administration of study product and/or CHMI are reasonably related in time, and the AE is more likely explained by study agent or CHMI than other causes.
- **Possibly Related**: The AE and administration of study product and/or CHMI are reasonably related in time, but the AE can be explained equally well by causes other than study agent or CHMI.
- **Not Related**: The AE is clearly explained by another cause not related to the study product or CHMI.

For purposes of preparing summary data reports in which AE attributions are simplified to "Related" or "Not Related", in this protocol, the "Definitely, Probably and Possibly" attributions above will be mapped to the "Related" category, while the "Unlikely/Probably Not Related" and "Not Related" attributions above will be mapped to the "Not Related" category. The definitions that apply when these two attribution categories alone are used are as follows:

- **Related**: There is a reasonable possibility that the AE may be related to the study product or CHMI.
- **Not Related**: There is not a reasonable possibility that the AE is related to the study product or CHMI.

Grading the Severity of an Adverse Event

The Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1 [July 2017] will be used to determine the severity grades of AEs in this protocol and is available from: https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

Several modifications were made to the table as follows:

- Weight loss will be recorded as an AE only if it is considered deleterious to the participant's health.
- For severity grading of the solicited bruising parameter at the product administration site, the definitions based on size of the largest diameter and listed for the "Injection Site Erythema or Redness" will be used. The severity grade definition for "Bruising" provided under the Dermatologic Clinical Conditions will be used only for unsolicited AEs involving bruising at other body locations.
- Creatinine changes will be graded on the basis of the upper limit of normal provided by the grading table and not change from baseline.
- Creatinine clearance changes will be graded according to ml/min provided by the grading table and not change from baseline.
- Subclinical CMP results for sodium, potassium, chloride, bicarbonate, BUN, and glucose will not be considered an AE unless Grade 2 or higher.

APPENDIX III: STUDY PRODUCT PREPARATION

1. Preparation for IV Administration

To prepare an IV infusion, the pharmacist will complete the sequence of steps outlined below.

1. Obtain a pre-filled, DEHP-free, 100 mL IV bag of 0.9% saline.
2. Remove the air from the IV bag.
3. Calculate the total dose needed to prepare L9LS in the 0.9% saline bag in order to achieve the ideal concentration of ≥ 2 mg/mL.

   The IV bag may be prepared with a higher volume than required (i.e. overfill) to ensure proper administration via volumetric pump.

   Maintaining-infusible volume of-L9LS at the minimum concentration of 2 mg/mL may cause the total L9LS dose in the bag to exceed the lower weight-based dose (e.g., 1 mg/kg).

   Do not infuse the entire volume of the IV bag if the total amount exceeds the weight-based dose of the subject.
4. Thaw and equilibrate vials on the bench at room temperature for 90 minutes. If vials are stored at 5°C ± 3°C, equilibrate for approximately 30 min at room temperature before use.
5. Gently swirl the vials for 30 seconds to mix while avoiding foaming. Vials should never be shaken.
6. Withdraw the necessary amount of L9LS and add it to the IV bag so that final concentration in bag is ≥ 2 mg/mL.
7. Add the syringe contents to the sterile bag of saline using good sterile compounding technique.
8. An in-line filter infusion set is required for IV product administrations and must comply with the following specifications: 1.2 micron polyethersulfone filter membrane, DEHP-free, latex-free (equivalent to B. Braun #473994 filter extension set). After the in-line filter is added to the tubing, the administration set must be primed.

Note: If the compounded IV preparation has been stored at 5°C ± 3°C, equilibrate for approximately 30 min at room temperature before use. The study product solution will typically be administered IV over about 15-30 minutes using a volumetric pump. The total time needed to administer the dose may be longer than 30 minutes based on factors such as subject tolerance. The mL/hr infusion rate may vary based on the total volume needed to administer a full dose.

IV bag prepared without overfill:

At the end of product administration, the IV administration set **must** be flushed with about 30 mL (or appropriate volume) of normal saline.

IV bag prepared with overfill:

At the end of product administration, the IV administration set should **not** be flushed with saline.

2. Preparation for SC or IM Administration

To prepare a SC or IM administration dose, the pharmacist will complete the sequence of steps as outlined in this section.

1. Calculate the total mg DP needed.
2. Thaw and equilibrate vials on the bench at room temperature for 90 minutes. If vials are stored at 5°C ± 3°C, equilibrate for approximately 30 min at room temperature before use.
3. Gently swirl the vials for 30 seconds to mix while avoiding foaming. Vials should never be shaken.
4. Withdraw the necessary amount of L9LS using a 5-micron filter needle (maximum syringe fill volume of 2.5 ml for SC and 1.0 mL for IM). Use a new filter needle for each syringe.
5. Prior to dispensing, discard the filter needle and replace it with a needle suitable for SC or IM injection.

Note: If SC or IM preparations have been stored at 5°C ± 3°C, equilibrate for approximately 30 min at room temperature before use.

PRINCIPAL INVESTIGATOR: Richard Wu, MD

STUDY TITLE: VRC 614 (000536): A Phase 1, Dose Escalation, Open-Label Clinical Trial with Experimental Controlled Human Malaria Infections (CHMI) to Evaluate Safety and Protective Efficacy of an Anti-Malaria Human Monoclonal Antibody, VRC-MALMAB0114-00-AB (L9LS), in Healthy, Malaria-Naive Adults

STUDY SITE: NIH / NIAID / VRC / Vaccine Evaluation Clinic (VEC)

Cohort: *Healthy volunteer*

Consent Version: *Version 2.0, November 3, 2021*

WHO DO YOU CONTACT ABOUT THIS STUDY?

Principal Investigator: Richard Wu, MD, [redacted]

Study Coordinator: Floreliz Mendoza, RN, [redacted]

KEY INFORMATION ABOUT THIS RESEARCH

The purpose of this consent form is to give you information to help you decide if you would like to be part of a research study at the National Institutes of Health (NIH). The decision to participate is your choice. This section provides information we believe is most helpful and important to you in making your decision. Additional information that may help you decide can be found in other sections of the document.

This is a study of an experimental drug called "L9LS". L9LS is a monoclonal antibody that targets malaria. **L9LS has not been tested in humans before this study**. We do not know if L9LS will protect you from malaria infection. There is no malaria in L9LS, so you cannot get the infection just by taking the experimental drug. You should not assume L9LS will protect you from malaria if you travel to a place where there is a risk of infection.

The main purpose of this study is to see if L9LS is safe and how your body responds to the antibody. This is the first time that L9LS will be given to people, and we do not know how your body will respond. We will follow everyone who gets L9LS for about 24 weeks.

If you have side effects from L9LS, we expect them to be like those that occur with other antibody products. These side effects include fever, chills, shaking, nausea, diarrhea, vomiting, pain, headache, dizziness, and tiredness. They usually occur within the first 24 hours after the antibody is given. Some antibody products have a risk of serious allergic reactions that can be life threatening. Although rare, other side effects that may occur are trouble breathing, itchiness, rash, hives, swelling, or chest pain, and you must reach out to the study clinicians right away if you have any of these serious side effects.

Another purpose of this study is to test if L9LS prevents you from getting malaria when you are bitten by mosquitoes that carry live malaria parasites. This is called a "malaria challenge" or a

controlled human malaria infection (CHMI). You must be available on the day of the CHMI if you are in a group taking part in the CHMI. Each person who takes part in the CHMI may get malaria infection, and we will follow everyone afterward for about 7 weeks. The CHMI will include participants who get a dose of L9LS and "control" participants who do not get L9LS.

Starting 7 days after the CHMI, you must come to the clinic every day for 11 days to be checked for malaria parasites through a blood test. Testing is done every day so that the level of malaria in your blood does not get to dangerous levels. **After the CHMI, it is important that you come to the clinic for your scheduled visits so that the level of malaria parasites in your blood does not increase to dangerous levels**.

At the first sign of malaria infection in your blood, we will treat you with a medication that will cure you. Even if the blood test is never positive, all who take part will get treated with a malaria medication at Day 21 after CHMI. We take this step to make sure that everyone is cured of malaria. The drugs that treat malaria may cause some side effects. Once you are treated, you will not be at risk for recurrence/reactivation of the infection from the CHMI. If you do not take part in the CHMI, you will not be at greater risk of getting malaria infection and will not need drugs that treat malaria.

During the study, we will collect blood samples from you. Some of your blood will be stored for future research. You will be compensated for your time and inconvenience for taking part in this study.

The study will last about 2 to 6 months, depending on your study group. During this time, you must use an effective form of birth control if able to become pregnant, must not travel to a malaria region, must not take antibiotic drugs starting 4 weeks before the beginning of the CHMI and during the CHMI (unless prescribed by a physician, in which case the study team must be notified) or donate blood for 3 years following participation in CHMI. These safety measures are further described below. All clinical study visits will take place at the NIH Clinical Center in Bethesda, Maryland. The CHMI will take place at the Walter Reed Army Institute of Research facility in Silver Spring, Maryland, and is also supported by the U.S. Department of Defense (DOD).

The remaining document will now describe the research study in more detail. This information should be considered before you make your choice. Members of the study team will talk with you about the information in this document. Some people have personal, religious, or ethical beliefs that may limit the kinds of medical or research interventions in which they would want to participate. Take the time you need to ask any questions and discuss this study with NIH staff, and with your family, friends, and personal health care providers.

IT IS YOUR CHOICE TO TAKE PART IN THE STUDY

You may choose not to take part in this study for any reason. If you join this study, you may change your mind and stop participating in the study at any time and for any reason. In either case, you will not lose any benefits to which you are otherwise entitled. However, to be seen at the NIH, you must be taking part in a study or are being considered for a study. If you do choose to leave the study, please inform your study team to ensure a safe withdrawal from the research.

WHY IS THIS STUDY BEING DONE?

Malaria is a disease that affects more than 250 million people throughout the world. The parasites that cause malaria are known as *Plasmodium*. They live in the mosquito saliva and are injected into the skin when a mosquito bites a human. This can cause malaria infection. Malaria occurs in most tropical parts of the world including Africa, Southeast Asia and South America. It is a serious threat to the local populations, to travelers and to military personnel stationed overseas. Although there are medicines to treat malaria, there is no vaccine that fully prevents infection and treatment is not easy to get in many areas of the world. If malaria is not treated right away, it can become a serious and sometimes deadly disease. If it is treated right away, it can be completely cured.

The purpose of this research study is to test a drug that could prevent malaria infection in humans called L9LS. L9LS is considered investigational, which means that it has not been approved by the U.S. Food and Drug Administration (FDA) to prevent malaria infection. It is a monoclonal antibody (mAb) that targets the parasites that cause malaria. Antibodies are naturally made by the immune system to fight infection by blocking germs (bacteria and parasites) like malaria. Monoclonal means that all the antibodies in L9LS are exactly the same.

L9LS was developed at the Vaccine Research Center (VRC) at NIH. It was made in a laboratory and looks like an antibody that your own body could make. It has shown promise for prevention of malaria in laboratory and animal studies, but it has not yet been studied in humans.

This is the first study to give L9LS to humans. We do not know if L9LS will protect you from malaria infection. You cannot get malaria from L9LS because there is no malaria in it. You should not assume L9LS will protect you from malaria.

The purpose of this research study is to see if L9LS is safe and how your body responds to it. We will give you a dose of L9LS and measure how much of it stays in your body over time. We also want to see the differences between getting L9LS as an infusion in a vein in your arm (intravenously, IV) as an injection under the skin (subcutaneously, SC) or as an injection into a muscle (intramuscularly, IM).

In this study, you will be exposed to malaria through bites from mosquitos infected with malaria parasites, if you are in Groups 1-5. This is called a "malaria challenge" or a "Controlled Human Malaria Infection" (CHMI).We do this to find out if L9LS prevents you from getting malaria after you are bitten by the infected mosquitoes in a controlled setting. We will monitor you closely and test your blood every day for many days to see if you get infected with malaria. Even if your test is negative, we will give everyone malaria treatment by 21 days after CHMI.

We are asking you to join this research study because you are a healthy adult between the ages of 18 and 50 who has never been infected with malaria. If you are in Groups 1-5, you must be willing to take part in the CHMI and comply with follow-up requirements after CHMI to be in this study. If you take part in the CHMI, you must also agree not to travel to a malaria endemic region during the whole study and not to donate blood to a blood bank for 3 years after CHMI.

WHAT WILL HAPPEN DURING THE STUDY?

This study has 6 groups as shown in the Study Schema table below. Groups 1, 2, 3, 4, and 6 will get different doses and/or routes of L9LS. Most people who get L9LS will get it by infusion into a vein (IV). Some people will get L9LS into the fat under the skin (SC) or into the muscle (IM).

A group of people called "control" participants will not get the study product but will take part in the CHMI. This group helps us make sure the mosquitos can infect people.

VRC 614 Study Schema				
Group	Subjects	L9LS Administration		CHMI
		Dose (mg/kg)	Route	
1	5	1	IV	X
2	4	5	IV	X
3	5	5	SC	X
4	4	20	IV	X
5	6[1]	Control		X
6	5	5	IM	N/A
Total	29	[1]Two (2) additional control subjects will be enrolled as CHMI back-ups		

If you decide to take part in this study, you will be asked to review and agree to this informed consent form and the procedures outlined within it. You will have completed the screening process which includes a physical exam and review of your medical history, vital signs and laboratory results. You must be healthy and qualify for enrollment before you can take part in this study.

The study will start with enrollments of people to the lowest dose of L9LS by IV and SC routes (1 mg/kg IV (Group 1) and 5 mg/kg SC (Group 3)). The next groups, 5 mg/kg IV (Group 2) and 20 mg/kg IV (Group 4), will open after the study team reviews available safety data and agrees that there are no safety concerns at the lower IV doses. Group 5 can be enrolled at any time. Group 6 will enroll after the IV and SC groups have received the study product and have undergone CHMI. Groups 1-5 will take part in the CHMI.

If you are in Group 5, you will be a control participant and will not get a dose of L9LS. After enrollment, we will check your health and draw your blood before the CHMI.

If you are female and able to become pregnant, you must use an effective method of birth control for the entire study. You will be given a pregnancy test before you get any dose of L9LS and before the CHMI. If you are pregnant, we will not give you L9LS and you cannot take part in the CHMI.

L9LS ADMINISTRATION

You will be in the clinic for about 8 hours on the day L9LS is given.

- Intravenous (IV) Dosing (Groups 1, 2, 4): We will place an IV line (thin tube) in a vein in your arm. The IV line will be attached to a bag that has L9LS mixed with a liquid called "normal saline" or salt water. It will flow into your vein for about 30 minutes. If you have side effects during the infusion, it may be slowed down or stopped as needed. At the end of your infusion, we will monitor you for any side effects. If you are the first person to get the first of a new dose level, you will be monitored for at least 2 hours. Everyone else will be monitored for at least 1 hour after getting L9LS.

  We will also place an IV line in your other arm for blood collection during the visit to avoid sticking you with a needle multiple times. We will draw your blood before and right after the infusion, and then 3 more times during the 4-6 hours after the infusion.

You will be allowed to go home about 4-6 hours after the infusion, as long as you do not have concerning side effects. If you have side effects, we will treat them. You will need to come back to the clinic 2 times during the same week for blood draws.

- Subcutaneous (SC) Dosing (Group 3): We will use a small needle to inject L9LS into the fatty tissue of your belly. We may use your arm or thigh area instead of your belly if those sites are more appropriate for your body. You will get 1 or 2 injections to get the full dose of L9LS. If you are the first person to get L9LS in this group, you will be monitored for at least 2 hours. Everyone else will be monitored for at least 1 hour after getting L9LS. If there are no safety concerns, you will be allowed to leave the clinic after the safety check. You will need to come back to the clinic3 times during the same week for blood draws.
- Intramuscular (IM) Dosing (Group 6): We will use a needle to inject L9LS into the muscle of your upper arm and/or thigh. You will get 2 to 4 injections to get the full dose of L9LS. If you are the first person to get L9LS in this group, you will be monitored for at least 2 hours. Everyone else will be monitored for at least 1 hour after getting L9LS. If there are no safety concerns, you will be allowed to leave the clinic after the safety check. You will need to come back to the clinic 3 times during the same week for blood draws.

We will give you a thermometer so that you can check your temperature every day for 7 days after you get L9LS. You will need to record your highest temperature daily and tell us about any symptoms you have. We will also give you a measuring tool so that you can measure any redness, swelling, or bruising you may have at the injection site. You will get a password to a secure website to record this information. If you do not have internet access, you may use a paper diary that we give you instead.

If you have any side effects or feel unwell after you get L9LS, you should tell a VRC nurse or doctor as soon as possible. You can reach the clinic staff by phone 24 hours a day. If you have symptoms, you may be asked to come into the clinic for an examination before your next scheduled visit. You may also stay overnight in the hospital, if needed. It is very important that you follow the instructions from the clinic staff

FOLLOW-UP AFTER L9LS ADMINISTRATION

The follow-up visits will last 30 minutes to 2 hours and allow us to check you for any health changes or problems. We will ask you how you are feeling and if you have taken any medications. We will measure your vital signs, and may perform a targeted physical exam based on how you are feeling. We will take about 1–11 tubes of blood (~ less than one half up to 6 tablespoons at each visit for safety and/or research tests. Blood draw volumes will be within NIH Clinical Center limits. We will tell you right away if any of your test results show a health problem. You might need to have extra clinic visits and laboratory tests if you have health changes that need to be checked.

Clinical studies follow a set schedule. This helps us answer the research questions. The visit schedule is a little flexible, but **it is important that you follow the schedule as closely as possible**. **You should try to not miss any visits.** You should contact the clinic staff as soon as possible if

you need to change the date or time of any study visit. When you complete this study, we may invite you to take part in another study for follow-up sample collection.

CONTROLLED HUMAN MALARIA CHALLENGE (CHMI) – GROUPS 1-5 ONLY

To learn if L9LS can prevent malaria infection, we will conduct a CHMI. The CHMI will be performed by U.S. Military scientists, physicians and other trained personnel who are experienced in conducting a CHMI under controlled conditions. It will take place at the Walter Reed Army Institute of Research (WRAIR) facility in Silver Spring, Maryland. The CHMI visit will last about 4 to 6 hours and begins very early in the morning.

During the CHMI, we will put mosquitoes carrying the malaria parasites into a cup. The cup is covered with nylon tulle netting and allows the mosquitoes to bite you under controlled conditions. They cannot escape from the cup. No more than 5 mosquitoes are put in the cup at one time. You will hold the cup against your arm for 5 minutes and then the mosquitos will be checked for blood feeding and presence of malaria parasites. If needed, more mosquitoes may be added until we are sure that a total of 5 mosquitoes have fed on your blood.

Follow up after the CHMI is very important so we can check your health. We know that it takes anywhere from 7-15 days to find malaria parasites in the blood. So, after the CHMI, we will call you by phone to check on you 2 times in the first week. Then, starting on day 7, you must come to the NIH Clinical Center every day for about 30-minute visits through day 17 so we can collect blood for diagnostic and research purposes. The visits may be longer if medical evaluation is needed. If you test positive for malaria, you will be treated right away with anti-malarial medication. We will also bring you back about 8 weeks after the CHMI to make sure you are cured. At day 21, anyone who still has a negative malaria test will be given antimalarial medication. This way we can make sure that anyone who might have malaria infection is treated, even if your tests are negative. If you are negative for malaria, we will call you by phone to check on you about 8 weeks after the CHMI

This type of CHMI has been done for over 35 years for many malaria studies. The mosquitoes that will be used are raised in a laboratory for CHMIs. They are infected with a specific strain of the malaria parasite (*Plasmodium falciparum*) that is known to be treatable with the anti-malaria medication we will give you. While the mosquitos are being grown, they feed on transfusion-quality human donor blood that has been screened following FDA requirements to make sure that the blood is not carrying any other infectious diseases. This type of malaria does not cause recurrent infections after you are treated.

HOW LONG WILL THE STUDY TAKE?

The study will last for about 24 weeks if you are in Groups 1, 2, 3, 4, and 6 that get L9LS. You will visit the NIH Clinical Center for about 11 or 12 study visits based on if you get L9LS by IV or SC/IM, respectively, and up to 15 visits for the CHMI follow-up if you are taking part in the CHMI. If you are in Group 5, which does not receive L9LS, the study will last for about 7 weeks after the CHMI. We will discuss the exact schedule and location of these visits with you.

HOW MANY PEOPLE WILL PARTICIPATE IN THIS STUDY?

We plan to enroll about 29 people. This includes about 23 people who will get L9LS and about 6 control participants. We may enroll up to 40 people if needed to complete the study and this includes 2 back-up control participants for the CHMI.

WHAT ARE THE RISKS AND DISCOMFORTS OF BEING IN THE STUDY?

POSSIBLE RISKS OF L9LS

This study is the first time that L9LS will be given to people. The information described below is taken from studies with other antibodies that are like L9LS and may work the same. Some of those antibodies are approved for use in people. Like other drugs, monoclonal antibodies can cause side effects, some of which can be serious. Most side effects occur within the first 24 hours after an antibody is given.

- Side effects to antibodies given by IV may include: fever, chills, shaking, nausea, vomiting, pain, headache, dizziness. More serious but rare side effects may occur, including trouble breathing, high or low blood pressure, itchiness, rash, hives, lip or face swelling, diarrhea, racing heart, or chest pain. These symptoms usually go away within a few minutes to hours after the product is given. We are giving L9LS at a controlled rate. If you develop symptoms while getting L9LS, tell the nurse right away. Slowing or stopping the flow rate may help improve the symptoms.
- Side effects to antibodies given by SC may include: mild itchiness, redness and/or swelling at the site of injection. Tiredness, muscle pain, and headache have also been reported. These symptoms usually go away within 1 to 2 days.
- Side effects to antibodies given IM include: mild itchiness, redness and/or swelling at the site of injection. Tiredness, muscle pain, and headache have also been reported. These symptoms usually go away within 1 to 2 days.

Some antibodies have a risk of serious allergic reactions that can be life threatening including:

- Anaphylaxis is one type of allergic reaction that may happen soon after an antibody is given. This reaction can include difficulty breathing, low blood pressure, hives, rash, or swelling in the mouth and face. This reaction is rare but can be life threatening. Participants will remain under observation in the time frame that this usually occurs.
- Serum sickness is a type of allergic reaction that may happen several days to weeks after an antibody is given. This reaction may include hives, rash, fever, enlarged lymph nodes,muscle pains, joint pains, chest discomfort or shortness of breath.

Some antibody products can increase the risk of serious infections. L9LS is not expected to increase the risk of serious infections because it attacks a parasite and does not target the human immune system.

In a lab study, L9LS attached to the salivary glands that produce saliva. This was a rare finding. We do not know if L9LS affects your salivary glands. We will be checking for any possible problems with your salivary glands during the study. If there is a concern for salivary gland

problems, we may ask an oral specialist to examine you and provide a recommendation for your care.

UNKNOWN RISKS

L9LS may have other side effects that are not yet known. Taking part in this study may affect your eligibility for future monoclonal antibody or malaria studies. We will give you any new information about risks or other information that may affect your decision to continue in the study as it becomes available. You may not donate blood while taking part in this study and you may not donate blood for one year after the date of your last dose of L9LS or three years after your last CHMI.

POSSIBLE RISKS OF IV, IM, OR SC DOSING

General risks of methods that use a needle include stinging, discomfort, pain, soreness, redness, bruising, swelling or a tiny cut at the needle insertion site.

POSSIBLE RISKS OF BLOOD DRAWING

Blood drawing may cause pain, bruising, and may cause a feeling of lightheadedness or fainting. Rarely, it may cause infection at the site where the blood is taken. An IV line will be placed in your vein for a few hours on a day L9LS is given by IV. Problems at the IV site are usually mild and may include pain, bruising, minor swelling, or bleeding. Rarely, there may be an infection, vein irritation, nerve problem, or blood clot.

POSSIBLE RISKS OF CHMI – GROUPS 1-5 ONLY

During the CHMI, you will be bitten by mosquitoes that carry live malaria parasites which cause malaria infection. We do not know if L9LS will protect people from malaria. If you did not receive any L9LS and are in the control group, you are expected to get malaria. If you get malaria, you may experience the following symptoms:

- Fever, chills, headache, dizziness, muscle aches, sweats, fatigue, insomnia
- Nausea, vomiting, stomach cramps, diarrhea
- Decrease in numbers of red blood cells, white blood cells, and platelets
- Enlarged liver or spleen

Symptoms are usually mild to moderate, but you may have some severe symptoms. You may have fevers for 1 to 3 days. You may miss time from work or school due to your illness. You will not be compensated for any loss of income for missing work. If malaria is not treated right away, it can lead to kidney, liver, heart or brain damage and death. The CHMI is considered to be safe because people are closely monitored and treated as soon as they are found to have malaria infection, but they must remain in close contact with the study team.

After the CHMI, it is important that you come to the clinic for your scheduled visits so that the level of malaria parasites in your blood does not increase to dangerous levels. From past studies we know that malaria parasites can be found in the blood anywhere from about 7 to 15 days after mosquito exposure. About half of the people infected with malaria parasites develop

fever that usually lasts less than 12 hours. Once treatment for malaria is started, the fever does not last longer than 48 hours.

Other symptoms of headache, nausea, vomiting, and loss of appetite may occur. These symptoms may last an average of 3 days, with a range of 1 to 6 days when treatment is started soon after malaria parasites are identified by blood tests. **Failure to return for testing or treatment after a CHMI can result in a serious case of malaria that is life-threatening.** For this reason, you must give the names and phone numbers of at least two emergency contacts to the study staff. We will contact them before the CHMI to confirm communication with them in case we are not able to reach you by phone, text, or email after CHMI.

Among the 2,700+ participants who have participated in a CHMI since 1971, two serious events have been reported. Both were cardiac events (chest pain) and occurred in people who got an investigational malaria vaccine. The pain was thought to be due to myocarditis (inflammation of the heart muscle). Myocarditis is a reported complication from vaccinations. Rarely, myocarditis has also been reported in association with naturally-acquired malaria infection.

These are the only two cases we know about in which a cardiac event occurred after CHMI. In the unlikely event that you develop myocarditis, you will be evaluated and followed by a cardiologist until resolution.

If you feel unwell at any time after the CHMI, you may be asked to remain in the clinic until you are checked by a study doctor. You might stay in the hospital overnight if needed.

POSSIBLE RISKS FROM TREATMENT FOR MALARIA – GROUPS 1-5 ONLY

Everyone who takes part in the CHMI will get antimalarial treatment by Day 21 after CHMI. Standard treatment for malaria takes 72 hours to complete. We will give you the medication at the first sign of infection in your blood. You should expect to have malaria symptoms for about 3 days. Only drugs approved by the U.S. FDA will be used for treatment of malaria. We will treat you with Malarone unless you have a known allergy. In that case, we would treat you with chloroquine or another suitable alternative. Any drugs given are effective in treating the type of malaria parasite used for the CHMI.

The drugs that treat malaria may also cause some side effects. Treatments and their side effects are described below:

1. The first line of treatment will be Malarone. If you get Malarone, you may have the following side effects:
    - Nausea, vomiting, abdominal pain, loss of appetite, diarrhea
    - Temporary elevation of liver function tests
    - Headache and coughing
    - Rarely, low blood count, oral irritation or ulcers, insomnia, fever, swelling, rash and hair loss
2. Another backup treatment option will be chloroquine. If you get chloroquine, you may have the following side effects:
    - Nausea, vomiting, abdominal pain, diarrhea, dizziness, sleep

disturbances and photosensitivity
- Headache, blurred vision, ringing in ears
- Itching, skin rash, and make conditions of psoriasis (itchy skin rash) and porphyria (rare disturbance of metabolism that can be seen as disorders of the skin or other organs) worse
- Long term use can cause permanent eye damage or deafness, but you will only be receiving a short course of treatment
- Rarely, there may be changes in electrocardiograms (test of heart's electrical activity) and low blood pressure

If you need treatment with any other antimalarial drug, we will give you information about the side effects of that drug. You can also take over-the-counter medicine, like acetaminophen (Tylenol) and/or ibuprofen for fever, headache or other symptoms of malaria.

MOSQUITO BITE SITE REACTIONS – GROUPS 1-5 ONLY

Local, allergic reactions are common after mosquito bites. You may have itching and raised, red swelling at the sites of the bites. These reactions usually develop quickly, go away 1 to 4 days after a mosquito bite, and do not need treatment. So far, no severe allergic reactions to mosquito bites have been reported in prior CHMI studies. You will be observed for 30 minutes after the last mosquito bite. We will check the bite area and watch for any severe allergic signs. We may give you a steroid cream to use on the skin reactions.

POSSIBLE RISKS FROM STORED SAMPLES

There is a small chance that information from your medical records could be given to someone who should not get it without your permission. It is possible for someone to use that information to discriminate against you when you apply for insurance or employment. Similar problems may occur if you give information about yourself or agree to have your medical records released.

POSSIBLE RISKS OF DATA SHARING

Information in the shared databases could be linked back to you and used to discriminate against you or your family. State and federal laws provide some protections against genetic and preexisting conditions discrimination.

POSSIBLE RISKS RELATED TO PREGNANCY

If you are able to become pregnant, we will do a pregnancy test before beginning this study. We will also give you a pregnancy test before you get L9LS and before CHMI. You must use effective birth control methods and try not to become pregnant while taking part in this study. If you become pregnant, there may be unknown risks to the fetus or unborn child, or risks that we did not anticipate. There may be long-term effects of the treatment being studied that could increase the risk of harm to a fetus. You must tell the study doctor if your birth control method fails while you are in the study. If you think or know you have become pregnant while taking part in this research study, please contact the research team member identified at the top of this document as soon as possible. You should not plan to become pregnant until you have completed participation in this study.

SAFETY MEASURES YOU SHOULD USE AS A PARTICIPANT IN THE STUDY

You should not expect L9LS to protect you from malaria in the future. You should assume that you are not protected from malaria. After leaving the study, you should follow your physician's instructions to prevent malaria infection. We also ask that you follow our instructions below:

- Travel: Do not travel outside the local area from the CHMI through 28 days after. Before or after this point, please let the study staff know about planned travels so we can schedule your visits and have contact information before you travel. We ask that you not travel to any areas with malaria during the entire period of the study. Country-specific informationcan be provided. This does not apply to Group 6.
- Use of Antibiotics: Avoid taking antibiotics starting 4 weeks before the CHMI and during the CHMI unless prescribed by a physician. Please notify the study team immediately if an antibiotic is prescribed for you or if you consider taking an antibiotic during the course of the study. This does not apply to Group 6.
- Blood Donation: You will not be permitted to donate blood for transfusion purposes while in the study, for 1 year after your L9LS administration and for 3 years after the CHMI. To make sure that blood is safe for donation, blood banks will not accept blood donations for 1 year after exposure to an investigational product (L9LS) and for 3 years from anyone who is infected with or treated for malaria.
- Mosquito Avoidance: For two weeks after the CHMI you should practice mosquito avoidant behaviors. This includes covering your skin when outside, avoiding outdoors at times mosquitoes are active (dusk, evening, dawn), using insect repellants appropriately on yourself and your clothes, and maintaining effective mosquito barriers in your home such as screen doors and windows. Clinical staff will cover these with you again in detail during the CHMI process. This does not apply to Group 6.

WHAT ARE THE BENEFITS OF BEING IN THE STUDY?

You will not benefit from being in this study.

Are there any potential benefits to others that might result from the study?

In the future, other people might benefit from this study because the information may help us learn more about preventing and treating malaria infection. Results from this study may also be used to help develop new products that target malaria or other infectious diseases in the future.

WHAT OTHER OPTIONS ARE THERE FOR YOU?

Before you decide whether or not to be in this study, we will discuss other options that are available to you. Instead of being in this study, you could choose not to take part. You may be eligible for other VRC studies.

DISCUSSION OF FINDINGS

New information about the study

If we find out any new information that may affect your choice to participate in this study, we will get in touch with you to explain what we have learned. This may be information we have learned while doing this study here at the NIH or information we have learned from other scientists doing similar research in other places.

Return of research results

At each visit you will be checked for any health changes or problems. Blood will be drawn at almost every study visit to either check on your health or collect samples for research. You will be told right away by phone call, text, or in person in the clinic if any of your test results show a health problem.

After the CHMI, we will draw your blood to test for malaria parasites. You will be told right away by phone, or in person in the clinic if we find that you have malaria infection.

We will use some of the blood samples to study how long L9LS remains in your body and if your body develops an immune response to L9LS and to the CHMI. We will also study the malaria parasites that we may find in your bloodstream after the CHMI if you get malaria infection. These tests are for research purposes only and are not for checking on your health. We will not give you these results.

The results of this study may be reported in medical journals, on the internet or at scientific meetings. We will give you information about how to find the study results once they are available.

EARLY WITHDRAWAL FROM THE STUDY

You may be removed from the research study by the researcher for any of the following reasons:

- Not keeping appointments or following study procedures;
- Getting a serious illness that needs ongoing medical care;
- Enrolling in another research study at the same time you are in this study;
- Becoming pregnant;
- The study is stopped or cancelled;
- The researcher believes that it is in your best interest to remove you from the study.
- The study is stopped by regulatory agencies, the study sponsor or study investigators. If this happens, we will tell you why.

You can stop taking part in the study at any time. However, if you decide to stop taking part in this study, you will be asked to keep follow up visits so we can check your health, especially if you got a dose of L9LS or take part in the CHMI. We may stop collecting samples that are for research purposes only.

We don't know if you will get malaria after the CHMI. If you choose to stop the study after the CHMI and before completion of monitoring for malaria infection, you will need to be treated for malaria by the study doctor regardless of whether you develop symptoms of malaria or parasites in your blood.

STORAGE, SHARING AND FUTURE RESEARCH USING YOUR SPECIMENS AND DATA

Will your specimens or data be saved for use in other research studies?

As part of this study, we are obtaining specimens and data from you. We will remove all the identifiers, such as your name, date of birth, address, or medical record number and label your specimens and data with a code so that you cannot easily be identified. However, the code will be linked through a key to information that can identify you. We plan to store and use these specimens and data for studies other than the ones described in this consent form that are going on right now, as well as studies that may be conducted in the future. These studies may provide additional information that will be helpful in understanding malaria, or other diseases or conditions. This could include studies to develop other research tests, treatments, drugs, or devices, that may lead to the development of a commercial product by the NIH and/or its research or commercial partners. There are no plans to provide financial compensation to you if this happens. Also, it is unlikely that we will learn anything from these studies that may directly benefit you.

By agreeing to take part in this study, you give permission for your coded specimens and data to be stored and used for future research as described above.

Will your specimens or data be shared for use in other research studies?

We may share your coded specimens and data with other researchers. If we do, while we will maintain the code key, we will not share it, so the other researchers will not be able to identify you. They may be doing research in areas that are similar to this study or in other unrelated areas. These researchers may be at NIH, other research centers and institutions, or commercial entities.

By agreeing to take part in this study, you give permission for your coded specimens and data to be shared with other researchers and used by these researchers for future research as described above.

If you change your mind and do not want us to store and use your specimens and data for future research, you should contact the research team member identified at the top of this document. We will do our best to comply with your request but cannot guarantee that we will always be able to destroy your specimens and data. For example, if some research with your specimens and data has already been completed, the information from that research may still be used. Also, for example, if the specimens and data have been shared already with other researchers, it might not be possible to withdraw them.

In addition to the planned use and sharing described above, we might remove all identifiers and codes from your specimens and data and use or share them with other researchers for future research at the NIH or other places. When we or the other researchers access your anonymized data, there will be no way to link the specimens or data back to you. We will not contact you to ask your permission or otherwise inform you before we do this. We might do this even if you answered "no" to the above questions. If we do this, we would not be able to remove your specimens or data to prevent their use in future research studies, even if you asked, because we will not be able to tell which are your specimens or data.

NIH policies require that your clinical and other study data be placed in an internal NIH database that is accessible to other NIH researchers for future research. Usually, these researchers will not have access to any of your identifiers, such as your name, date of birth, address, or medical record number; and your data will be labeled with only a code. We cannot offer you a choice of whether your data to be placed in this database or not. If you do not wish to have your data placed in this database, you should not enroll in this study.

GENETIC TESTING

Some of the blood drawn from you during this study will be used for genetic tests. Some genetic tests are done in research studies to see if there are genetic difference in immune responses. Your blood sample used in these genetic tests will not have your name on it, and the results will not be in your medical record.

How long will your specimens and data be stored by the NIH?

Your specimens and data may be stored by the NIH indefinitely.

Risks of storage and sharing of specimens and data

When we store your specimens and data, we take precautions to protect your information from others that should not have access to it. When we share your specimens and data, we will do everything we can to protect your identity, for example, when appropriate, we remove information that can identify you. Even with the safeguards we put in place, we cannot guarantee that your identity will never become known, or someone may gain unauthorized access to your information. New methods may be created in the future that could make it possible to re-identify your specimens and data.

PAYMENT

Will you receive any type of payment for taking part in this study?

You will be compensated for your time and inconvenience by the NIH Clinical Research Volunteer Program per NIH policies and guidelines. It is possible that you may have some expenses that are not covered by the compensation provided.

The compensation for specific study visits is as follows:

- $430 for the study visit that includes IV administration of L9LS
- $375 for the study visit that includes SC or IM administration of L9LS $455 for the malaria challenge (CHMI) with pre-CHMI clinic visit and activities
- $25 total for the timely completion of all 7 days of an electronic diary
- $200 for a scheduled follow-up visit that includes blood draw
- $85 for all other clinic visits that do not include blood draws

Total compensation for completion of all study visits including CHMI is between $4195 and $5950 if you get L9LS by IV and between $4340 and $6140 if you get L9LS by SC. Compensation for the IM group is around $2800. Compensation for CHMI visits for the control group is between about $1625 and $3425. The total compensation you get is based on the number and type of study

visits you complete. If you are unable to finish the study, you will get compensation only for the study visits you completed.

You will get the compensation about 2 weeks after each completed visit by direct deposit into a bank account that you specify to the Volunteer Payment Office.

The study team will collect social security numbers from research participants for purposes of compensation. Participants can withhold their social security numbers and still participate in the research study; however you may not be able to receive compensation if you do so.

With few exceptions, study compensation is considered taxable income that is reportable to the Internal Revenue Service (IRS). A "Form 1099-Other Income" will be sent to you if your total payments for research participation are $600 or more in a calendar year. If you have unpaid debt to the federal government, please be aware that some or all of your compensation may be automatically reduced to repay that debt on your behalf.

REIMBURSEMENT

Will you receive reimbursement or direct payment by NIH as part of your participation?

This study does not offer reimbursement for participants, or payment of, hotel, travel, or meals.

COSTS

Will taking part in this research study cost you anything?

NIH does not bill health insurance companies or participants for any research or related clinical care that you receive at the NIH Clinical Center.

CONFLICT OF INTEREST (COI)

The NIH reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a COI Guide. You may ask your research team for a copy of the COI Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines or the guidelines of their home institution, but they do not need to report their personal finances to the NIH.

The NIH and the research team for this study have developed the investigational product, L9LS, being used in this study. This means it is possible that the results of this study could lead to payments to NIH. By law, the government is required to share such payments with the employee inventors. You will not receive any money from the development of L9LS.

CLINICAL TRIAL REGISTRATION AND RESULTS REPORTING

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results, once they are available. You can search this website at any time.

CONFIDENTIALITY PROTECTIONS PROVIDED IN THIS STUDY

Will your medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The NIH and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- NIH Intramural Institutional Review Board
- The study Sponsor (VRC) or their agent(s)
- United States Army Medical Research and Development Command (USAMRDC) representatives

The researchers conducting this study and the NIH follow applicable laws and policies to keep your identifying information private to the extent possible. However, there is always a chance that, despite our best efforts, your identity and/or information about your participation in this research may be inadvertently released or improperly accessed by unauthorized persons.

In most cases, the NIH will not release any identifiable information collected about you without your written permission. However, your information may be shared as described in the section of this document on sharing of specimens and data, and as further outlined in the following sections.

Further, the information collected for this study is protected by NIH under a Certificate of Confidentiality and the Privacy Act.

Certificate of Confidentiality

To help us protect your privacy, the NIH Intramural Program has received a Certificate of Confidentiality (Certificate). With this certificate, researchers may not release or use data or information about you except in certain circumstances.

NIH researchers must not share information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if requested by a court.

The Certificate does not protect your information when it:

1. is disclosed to people connected with the research, for example, information may be used for auditing or program evaluation internally by the NIH; or
2. is required to be disclosed by Federal, State, or local laws, for example, when information must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA);
3. is for other research;
4. is disclosed with your consent.

The Certificate does not prevent you from voluntarily releasing information about yourself or your involvement in this research.

The Certificate will not be used to prevent disclosure to state or local authorities of harm to self or others including, for example, child abuse and neglect, and by signing below you consent to those disclosures. Other permissions for release may be made by signing NIH forms, such as the Notice and Acknowledgement of Information Practices consent.

Privacy Act

The Federal Privacy Act generally protects the confidentiality of your NIH medical information that we collect under the authority of the Public Health Service Act. In some cases, the Privacy Act protections differ from the Certificate of Confidentiality. For example, sometimes the Privacy Act allows release of information from your record without your permission, for example, if it is requested by Congress. Information may also be released for certain research purposes with due consideration and protection, to those engaged by the agency for research purposes, to certain federal and state agencies, for HIV partner notification, for infectious disease or abuse or neglect reporting, to tumor registries, for quality assessment and medical audits, or when the NIH is involved in a lawsuit. However, NIH will only release information from your medical record if it is permitted by both the Certificate of Confidentiality and the Privacy Act.

POLICY REGARDING RESEARCH-RELATED INJURIES

The NIH Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the NIH, the NIH Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

FOR INJURIES RELATED TO CHMI

If you are injured because of your participation in this research during the CHMI and you are a DOD healthcare beneficiary (e.g., active duty in the military, military spouse or dependent, retiree), you are entitled to medical care for your injury within the DOD healthcare system, as long as you remain a DOD healthcare beneficiary.

If you are injured because of your participation in this research during the CHMI and you are not a DOD healthcare beneficiary, you are entitled to medical care for your injury at a DOD hospital or clinic, but such care for your injury at DOD hospitals or clinics may be time-limited, and your insurance may be billed. It cannot be determined in advance which DOD hospital or clinic will provide care. If you obtain care for research-related injuries outside of a DOD hospital or clinic, you or your insurance will be responsible for medical expenses.

For DOD healthcare beneficiaries and non-DOD healthcare beneficiaries: Transportation to and from hospitals or clinics will not be provided. No reimbursement is available if you incur medical expenses to treat research-related injuries. No compensation is available for research-related injuries. You are not waiving any legal rights. If you believe you have sustained a research-related injury, please contact the Principal Investigator (PI). If you have any questions, please contact the PI.

PROBLEMS OR QUESTIONS

If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Richard Wu, MD at [redacted] Other researchers you may call are: Floreliz Mendoza, RN or Lasonji Holman, FNP at [redacted] You may also call the NIH Clinical Center Patient Representative at [redacted] or the NIH Office of IRB Operations at [redacted] if you have a research-related complaint or concern.

CONSENT DOCUMENT

Please keep a copy of this document in case you want to read it again.

Adult Research Participant: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I consent to participate in this study.

Signature of Research Participant	Print Name of Research Participant	Date

Investigator:

Signature of Investigator	Print Name of Investigator	Date

Witness should sign below if either:

1. **A short form consent process has been used to enroll a non-English speaking subject or**
2. **An oral presentation of the full consent has been used to enroll a blind or illiterate subject**

Signature of Witness	Print Name of Witness	Date

NIH ADMINISTRATIVE SECTION TO BE COMPLETED REGARDING THE USE OF AN INTERPRETER:

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent and served as a witness. The investigator obtaining consent may not also serve as the witness.

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent but did not serve as a witness. The name or ID code of the person providing interpretive support is: _____.