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Supplementary appendix

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VACCINE RESEARCH CENTER

Protocol VRC 608
(NIH 18-I-0069)

A PHASE I, OPEN-LABEL, DOSE-ESCALATION STUDY OF THE SAFETY AND PHARMACOKINETICS OF A HUMAN MONOCLONAL ANTIBODY, VRC-EBOMAB092-00-AB (MAB114), ADMINISTERED INTRAVENOUSLY TO HEALTHY ADULTS

Study Product Provided by:
Vaccine Research Center (VRC)
National Institute of Allergy and Infectious Diseases (NIAID)
National Institutes of Health (NIH)
Bethesda, MD

Clinical Trial Sponsored by:
NIAID/VRC/NIH, Bethesda, Maryland

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ABBREVIATIONS

Abbreviation	Term
ACE	Angiotensin converting enzyme
ADA	anti-drug antibody
AE	adverse event
ALT	alanine aminotransferase
AoU	Assessment of Understanding
AUC	area under the curve
β-HCG	human chorionic gonadotropin
BDBV	Species *Bundibugyo Ebolavirus*
C	Celsius
CBC	complete blood count
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practice
CI	confidence interval
CL	clearance
Cmax	maximum concentration
CMP	comprehensive metabolic panel
CRS	cytokine release syndrome
CTP	Clinical Trials Program (VRC)
DAIDS	Division of AIDS
EBOV	Species *Zaire Ebolavirus*
EDTA	Ethylenediaminetetraacetate
EHF	Ebola hemorrhagic fever
EIA	enzyme immunoassay
ELISA	enzyme-linked immunosorbent assay
EOI	end of infusion
EVD	Ebola virus disease
F	Bioavailability
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLT	Green Lithium Heparin Tube
GP	glycoprotein
HBcAb	Hepatitis B core antibody
HCV Ab	Hepatitis C virus antibody
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HRPP	Human Research Protections Program
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICTV	International Committee on the Taxonomy of Viruses
IgG	Immunoglobulin G

Abbreviation	Term
IgM	Immunoglobulin M
IND	Investigational New Drug
IRB	Institutional Review Board
IRS	Internal Revenue Service
IV	Intravenous
Kg	Kilogram
L	Liter
LIMS	Laboratory Information Management System
λz	terminal slope of concentration vs time profile
MAb	monoclonal antibody
mcg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
mL	Milliliter
mm	Millimeter
mM, mmol	Millimole
MO	Medical Officer
MSD	Meso Scale Discovery
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NIH CC	National Institutes of Health Clinical Center
NHP	Non-Human primate
OHRP	Office for Human Research Protections
PBMC	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PES	polyethersulfone
PI	Principal Investigator
PK	Pharmacokinetic
PSRT	Protocol Safety Review Team
Q	Inter-compartmental clearance
QA	quality assurance
RESTV	Species *Reston Ebolavirus*
RNA	ribonucleic acid
SAE	serious adverse event
SST	serum separator tube
SUDV	Species *Sudan Ebolavirus*
SUSAR	suspected, unexpected and serious adverse reaction
SWFI	sterile water for injection
TAFV	Species *Taï Forest Ebolavirus*
$T_{½}$	half-life
Tmax	time of maximal concentration (Cmax)
ULN	upper limit of normal
UP	unanticipated problem
UPnonAE	unanticipated problem that is not an adverse event

Abbreviation	Term
USP	United States Pharmacopeia
VCMP	Vaccine Clinical Materials Program
Vd	volume of distribution
VITL	Vaccine Immunology Testing Laboratory
VRC	Vaccine Research Center
WBC	white blood cell
WHO	World Health Organization
Wk	week

PRÉCIS

VRC 608: A Phase I, Open-Label, Dose-Escalation Study of the Safety and Pharmacokinetics of a Human Monoclonal Antibody, VRC-EBOMAB092-00-AB (MAb114), Administered Intravenously to Healthy Adults

Study Design: VRC 608 is the first-in-human Phase I study to examine safety, tolerability and pharmacokinetics of the monoclonal antibody (MAb), VRC-EBOMAB092-00-AB (MAb114). MAb114 will be administered as a single dose. The hypotheses are: 1) MAb114 administration to healthy adults will be safe by the intravenous (IV) route; and 2) MAb114 will be detectable in human sera with a definable half-life. The primary objectives are to evaluate the safety and tolerability of MAb114 in healthy adults. Secondary objectives will evaluate the pharmacokinetics of MAb114 and the potential to detect an anti-drug antibody response to MAb114.

Product Description: MAb114 is a human IgG1 MAb targeted to the *Zaire ebolavirus* (EBOV) glycoprotein (GP). It was developed by the VRC/NIAID/NIH and manufactured at Cook Pharmica LLC d.b.a. Catalent Indiana, LLC (Bloomington, IN) under current Good Manufacturing Practice (cGMP) regulations. MAb114 is supplied as a lyophilized product in a glass vial at 400 mg per vial with target overfill to 425 mg per vial.

Subjects: Up to 30 healthy adults, 18-60 years of age.

Study Plan: This is an open-label, dose-escalation study of MAb114 administered by IV infusion at dosages of 5, 25 and 50 mg/kg (Groups 1-3). Enrollment will begin with the lowest dose group. Following the first product administration in each group, the study team will wait at least 3 days before administering MAb114 to a second subject within the same group. Dose-escalation evaluations will occur to ensure the safety data support proceeding to the higher doses. Solicited reactogenicity following product administration will be evaluated using a 3-day diary. Assessment of safety will include clinical observation and monitoring of serum hematological and chemical parameters at defined timepoints throughout the study.

VRC 608 Study Schema		
Group	**Subjects**	**Dose and Route (Day 0)**
1	3	5 mg/kg IV
2	5	25 mg/kg IV
3	10	50 mg/kg IV
Total*	18	*A minimum of 18 subjects will be enrolled. Enrollment up to a total of 30 subjects is permitted if additional subjects are necessary for safety or pharmacokinetic (PK) evaluations.

Study Duration: Subjects will be followed for 24 weeks after the study product administration.

1. INTRODUCTION

Ebolavirus is a large, negative-strand ribonucleic acid (RNA) virus composed of 7 genes encoding viral proteins, including a single glycoprotein (GP) [1-3]. Ebolavirus is one of three genera in the Filoviridae family, which along with Marburgvirus, is known to induce viral hemorrhagic fever. In 2013, the International Committee on the Taxonomy of Viruses (ICTV) Filoviridae Study Group and other experts published an updated taxonomy for filoviruses. Five distinct species in the genus Ebolavirus have been implicated as the etiological agent of Ebolavirus disease (EVD), formerly known as Ebola hemorrhagic fever (EHF) in humans: Bundibugyo (BDBV), Reston (RESTV), Sudan (SUDV), Taï Forest (TAFV), and Zaire (EBOV) [4]. The BDBV, EBOV, and SUDV strains have been associated with large EVD outbreaks in Africa, with reported case fatality rates of up to 90% [5].

Ebolavirus was first described in 1976 near the Ebola River in the Democratic Republic of Congo (DRC). Since 1976, there have been multiple Ebola outbreaks with cases detected in many countries [6]. The largest EVD outbreak occurred in 2014 in West Africa and resulted in over 28,000 reported EVD cases and over 11,000 deaths [7]. EVD cases in persons who traveled from endemic areas were also reported in Italy, Spain, the United States (US) and the United Kingdom (UK) [6]. While the World Health Organization (WHO) declared an end to the EVD public health emergency in March 2016, small outbreaks continue to occur [7]. Given the frequency of international travel, EVD remains a global threat to public health.

Transmission of Ebolavirus to humans is not yet fully understood, but is likely due to incidental exposure to infected animals [8-10], through direct contact with blood, secretions, organs or other bodily fluids of infected people (alive and dead); and through indirect contact with environments contaminated by such fluids [5]. People are infectious for as long as their blood and secretions contain the virus. Men who have recovered from the disease can still transmit the virus through their semen for up to 7 weeks after recovery from illness [5], [11, 12].

EVD has an incubation period of 2 to 21 days (7 days on average, depending on the strain) followed by a rapid onset of non-specific symptoms such as fever, extreme fatigue, gastrointestinal complaints, abdominal pain, anorexia, headache, myalgias and/or arthralgias. These initial symptoms, which last for about 2 to 7 days, are followed by more severe symptoms related to hemorrhagic fever (e.g., hemorrhagic rash, epistaxis, hematuria, hemoptysis, hematemesis, melena, conjunctival hemorrhage, tachypnea, confusion, somnolence, hearing loss, and in some cases, both internal and external bleeding) and accompanied with low white blood cell (WBC) and platelet counts and elevated liver enzymes [5]. These symptoms generally last for about 7 to 14 days. Death can occur 6 to 16 days after the onset of symptoms, manifested by vomiting and diarrhea resulting in dehydration, shock and then multi-organ failure [8, 13].

Immunoglobulin M (IgM) antibodies to the virus appear 2 to 9 days after infection, followed by immunoglobulin G (IgG) antibodies at approximately 17 to 25 days after infection; the latter coinciding with the recovery phase [14]. In survivors of EVD, both humoral and cellular immunity are detected; however, their relative contribution to protection is unknown [14, 15].

Currently, no Food and Drug Administration (FDA)-approved therapies or licensed vaccines exist for any member of Filoviridae family of viruses.

1.1 Study Rationale

1.1.1 Passive Immunization with an Ebola-specific Antibody: MAb114

The Vaccine Research Center (VRC), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH) has developed an EBOV neutralizing MAb, VRC-EBOMAB092-00-AB (MAb114), targeted against the Ebolavirus Zaire GP. This MAb was identified from a subject infected with Ebolavirus during the 1995 outbreak in Kikwit, Democratic Republic of Congo, and who maintained circulating antibody for more than 10 years after infection [16]. MAb114 was selected following isolation and screening of a panel of memory B-cells based on its binding to the Ebolavirus GP and *in vitro* neutralization potential [16], [17]. Rhesus macaques passively immunized with MAb114 up to five days post-challenge with a lethal dose of EBOV were protected from EVD, suggesting its potential therapeutic potential in humans with EVD [16]. In earlier reports, cocktails of different MAbs have been tested in non-human primates (NHPs) and in a small number of humans; however, none have been proven to effectively treat EVD [18, 19].

The 2014 outbreak underscored the importance of a therapeutic strategy for populations when widespread vaccination coverage is not available or feasible such as when there are limited public health resources. Based on its *in vitro* activity and previous experience with other MAbs against EVD, the rationale for development of MAb114 is to provide a simplified therapeutic product and/or dosing regimen for EVD, identify mechanism(s) of EVD protection and explore development for potential stockpiling [20].

This Phase I study, VRC 608, is primarily directed at evaluation of the safety and pharmacokinetics of MAb114, which may provide therapeutic benefit with a single infusion in cases of EBOV exposure/infection.

1.1.2 Rationale for Dose and Administration Route Selection

Preclinical data in the NHP animal model informed the doses of MAb114 (5-50 mg/kg) that will be evaluated. In the GLP toxicity study, MAb114 doses ranging from 50 to 500 mg/kg/ week were well-tolerated, with MAb114 demonstrating linear kinetics and a 7-15-day half-life. Preliminary evidence in a NHP model of EVD showed a 50 mg/kg dose of MAb114 was protective to NHPs when administered up to five days post-EBOV challenge [16]. Moreover, a 25 mg/kg dose is important to explore because PK data on a 25mg/kg dose is valuable should future, planned dose-down studies in an NHP dose-down lethal challenge establish protection.

In an epidemic situation, application of effective protection measures against EBOV infection is urgent for exposed individuals. MAb114 will be administered by IV infusion to accelerate delivery as passive immunization studies with other MAbs developed by the VRC has shown antibody concentration peaks within hours after IV administration [21].

Refer to the Investigator's Brochure (IB) for more information on these proof-of-concept preclinical studies.

1.2 MAb114 Specific Research Laboratory Assessments

Research assays designed to characterize the investigational product rather than assess the health of the subjects are described below.

Research laboratory assessments in this Phase I study will include:

- MAb114 PK determinations as measured by enzyme-linked immunosorbent assay (ELISA),
- Detection of anti-drug antibody (ADA) to MAb114,
- Measurement of EBOV envelope GP-specific binding antibody by ELISA, and
- Ex vivo neutralization potential of MAb114 post-infusion as an exploratory evaluation.

De-identified stored samples may also be used later to further evaluate pharmacokinetics and to elucidate genetic factors associated with MAb114 pharmacokinetics.

Testing will be performed at the Vaccine Immunology Testing Laboratory (VITL) (known formerly as the NIAID Vaccine Immune T-Cell and Antibody Laboratory or NVITAL), in research laboratories at the VRC, Laboratory of Immunology, Biodefense Research Section, NIAID, NIH or by other approved collaborators.

1.3 Preclinical Toxicology Study of VRC-EBOMAB092-00-AB (MAb114)

A 4-week repeat dose intravenous toxicity study of MAb114 in male and female rhesus monkeys was performed by CiToxLAB North America (Québec, Canada) in accordance with Good Laboratory Practice (GLP) regulations. Treatment with IV-administered MAb114 at doses of 50 mg/kg once weekly, 50 mg/kg three times per week, and 500 mg/kg once weekly resulted in detectable concentrations of MAb114 at the end of the 8-week recovery period. There were no MAb114-related mortalities, clinical signs, or changes in body weight parameters following either one or three times weekly slow bolus IV infusions of MAb114 at 50 mg/kg (50 and 150 mg/kg/week, respectively) or weekly IV infusion of MAb114 at 0 or 500 mg/kg (500 mg/kg/week).

There were no MAb114-related effects on safety pharmacology parameters and no MAb114-related findings in eye exams. Hematology, coagulation and urinalysis parameters were not impacted by the MAb114 treatment. Clinical chemistry evaluations revealed non-adverse MAb114-related increases in serum globulins and total proteins with a secondary reduction in A/G ratio in individual animals, mainly in monkeys administered 500 mg/kg/week at Day 25. These findings were considered secondary to the administration of a high dose of a human immunoglobulin and were generally reversible upon cessation of dosing.

Details on preclinical studies conducted with MAb114 can be found in the IB.

1.4 *In Vitro* Safety Studies

The list of *in vitro* preclinical safety studies performed to assess potential off target binding of MAb114 are summarized in **Table 1**. Refer to the IB for more information about these studies.

Table 1: *In Vitro* Preclinical Safety Studies

Study Purpose	Study Outcome
Assessment of anti-phospholipid reactivity	MAb114 does not react to phospholipids.
Assessment of binding to a human epithelial cell line (HEp-2) by Immunohistochemistry	MAb114 does not bind to HEp-2 cells.
Assessment of potential "off target" binding in a GLP tissue cross-reactivity study with normal adult human tissues	To determine the potential cross reactivity of MAb114 binding, varying concentrations of MAb114 (1 and 10 mcg/mL) were applied to cryosections from a full panel of normal human adult tissues. Specific MAb114 staining was not observed in any tissue evaluated. The cytoplasmic or extracellular staining observed in multiple tissue elements was also noted on control slides and thus attributed to the secondary antibody. Overall, *in vitro* tissue cross-reactivity evaluations failed to identify potential tissue sites or organ systems for MAb114 binding in humans.

1.5 Non-Human Primate (NHP) Studies of VRC-EBOMAB092-00-AB (MAb114)

Non-GLP studies of MAb114 have been completed in NHPs to assess for preclinical evidence of potential efficacy for treatment of EVD. **Table 2** summarizes the studies performed and supports the plan to evaluate up to 50 mg/kg dose administered IV as a dose range of potential interest for a therapeutic indication.

Table 2: Preclinical proof-of-concept studies performed with MAb114 in NHP

Study Purpose	Study Outcome
Demonstration of protection with 3 doses of MAb114 administered at 3 different timepoints 24 hours apart starting one day after challenge with lethal dose of EBOV in female rhesus macaques	100% (3/3) of the female rhesus macaques infected with EBOV were protected from mortality when dosed with a 50 mg/kg IV dose of MAb114 administered 24, 48 and 72 hours post-challenge with EBOV. Control animal succumbed. [16]
Demonstration of protection with 3 doses of MAb114 administered at 3 different timepoints 24 hours apart starting five days after challenge with lethal dose of EBOV in female rhesus macaques	100% (3/3) of the female rhesus macaques infected with EBOV were protected from mortality when dosed with a 50 mg/kg IV dose of MAb114 administered 120, 144 and 168 hours post-challenge with EBOV. Control animal succumbed. [16]
Demonstration of protection with a single dose of MAb114 administered five days after challenge with lethal dose of EBOV in female rhesus macaques.	100% protection (3/3) from mortality demonstrated for a single 50 mg/kg dose administered IV five days post-challenge with EBOV. Control animal succumbed [data not published].
Demonstration of protection with a single dose of MAb114 administered five days after challenge with lethal dose of EBOV in female rhesus macaques.	100% protection (3/3) from challenge demonstrated for a single 30 mg/kg dose administered IV five days post-challenge with EBOV. Control animal succumbed [data not published].

1.6 Previous Human Experience

1.6.1 Human Experience with MAb114

As of 7/24/2018, 13 subjects have been enrolled and received one dose of MAb114 administered IV: 3 subjects received 5 mg/kg, 5 subjects received 25 mg/kg, and 5 subjects received 50 mg/kg. Overall, 13 product administrations have been completed.

There have been no serious adverse events (SAEs). Overall, 2 of 13 subjects (15.4%) have had one or more unsolicited adverse events (AEs) reported, with maximum severity being Grade 1 for 1 subject and Grade 2 for 1 subject, and all assessed as not related to the study product.

Product administrations have been well tolerated. No systemic or local reactogenicity symptoms were reported during the 30-minute MAb114 infusions.

Overall, 13 subjects completed diary cards. There were no reported or observed solicited local reactions in the 7 days after product administration. Regarding solicited systemic events, 3 of 11 subjects (23.1%) reported one or more mild systemic signs or symptoms in the 3 days after IV product administration. This included mild symptoms of malaise (n=2), myalgia (n=2), headache (n=3), chills (n=2), nausea (n=2), and joint pain (n=2).

1.6.2 Human Experience with Other Ebola-Specific Antibodies

Development and limited testing of other therapeutic MAbs indicated that these MAbs may have an acceptable safety profile in EVD-infected humans [18]. The triple monoclonal antibody product, ZMapp™, was administered to infected individuals during the recent 2014 outbreak demonstrating that MAbs have been tested in the treatment of EVD. Although efficacy was not demonstrated, the product was shown to be safe [19].

Recently data has been published on a new, co-formulated cocktail of three MAbs, REGN3470-3471-3479, targeting three non-overlapping epitopes on Ebolavirus glycoprotein. The product was developed by the Regeneron Pharmaceuticals, Tarrytown, NY, and was shown to be safe and well tolerated in a Phase 1 study in healthy adults [22].

2. STUDY PRODUCT

The study product, VRC-EBOMAB092-00-AB (MAb114) was developed by the VRC, NIAID, NIH (Bethesda, MD) and manufactured under cGMP by Cook Pharmica LLC d.b.a. Catalent Indiana, LLC (Bloomington, IN) operating under contract by MedImmune LLC (Gaithersburg, MD). MAb114 is a human IgG1 MAb targeted against the glycan cap and core domains in the GP1 subunit of *Zaire* EBOV GP [16].

The study product was produced using recombinant DNA technology. Following identification of the MAb114 memory B cell clone, heavy and light chain sequences were obtained by PCR amplification and DNA sequencing. Heavy and light chain sequences were cloned into an expression vector at Cellca GmbH (Laupheim, Germany). This expression vector was used to generate a stably transfected Chinese Hamster Ovary (CHO) DG44 cell line for use in cGMP manufacture.

The bulk lot of the drug substance was manufactured at Cook Pharmica LLC d.b.a. Catalent Indiana, LLC (Bloomington, IN) by purifying antibody produced from the stably transfected DG44 cell line. The drug substance was formulated, sterilized by membrane filtration, filled into glass vials, and lyophilized. The lyophilized product contains 400 mg of drug substance per vial with

target overfill to 425 mg per vial. Filled vials were transferred to the Vaccine Clinical Materials Program (VCMP), Leidos Biomedical Research, Inc. (Frederick, MD) for labeling. Vials are reconstituted prior to use. Reconstitution will involve addition of sterile water for injection (SWFI). The reconstituted product will nominally contain a 50 mg/mL concentration of MAb114 in 20 mM Histidine/Histidine HCl, 240 mM Sucrose, 0.02% Polysorbate 80, at pH 6.0. Vials are intended for single-use only and thus do not contain a preservative.

Details on MAb114 composition and manufacturing are provided in the IB. Quality Assurance (QA) lot release testing by the manufacturer and ongoing stability programs verify conformance to product specifications throughout trial conduct.

3. STUDY OBJECTIVES

3.1 Primary Objectives

- To evaluate the safety and tolerability of MAb114 administered as a single dose at 5 mg/kg IV to healthy adults.
- To evaluate the safety and tolerability of MAb114 administered as a single dose at 25 mg/kg IV to healthy adults.
- To evaluate the safety and tolerability of MAb114 administered as a single dose at 50 mg/kg IV to healthy adults.

3.2 Secondary Objectives

- To evaluate the pharmacokinetics of MAb114 at each dose level at representative timepoints throughout the study.
- To determine whether anti-drug antibody to MAb114 can be detected in recipients of MAb114.

3.3 Exploratory Objectives

- To evaluate for evidence of GP-binding activity of MAb114 in samples collected at representative timepoints throughout the study.
- To evaluate for evidence of functional neutralization activity of MAb114 in samples collected at representative timepoints throughout the study.
- Genetic factors associated with MAb114 pharmacokinetics may also be evaluated.

4. STUDY DESIGN

This is an open-label, dose-escalation study to examine the safety, tolerability, and PK of MAb114 in healthy adults. The primary hypothesis is that MAb114 administration will be safe by the IV route. The secondary hypothesis is that MAb114 will be detectable in human sera with a definable half-life. The study schema is shown in **Table 3**.

Table 3: VRC 608 Study Schema

Group	Subjects	Administration Schedule
		Day 0
1	3	5 mg/kg IV
2	5	25 mg/kg IV
3	10	50 mg/kg IV
Total*	18	*A minimum of 18 subjects will be enrolled. Enrollment up to a total of 30 subjects is permitted if additional subjects are necessary for safety or PK evaluations.

Enrollment will begin in the 5 mg/kg IV dose group (Group 1). Following the first product administration for each group, the study team will wait at least 3 days before administering MAb114 to additional subjects within that group. Dose escalation and subject enrollment into Groups 2 and 3 may proceed after interim safety reviews for the lower dose group as described in Section 4.3.

Safety review decisions and the status of the enrollment process will be presented to the Protocol Safety Review Team (PSRT) throughout the trial and discussed during the safety review meetings as described in Section 8.8.

Subjects will be expected to be available for follow-up visits during the 24 weeks of study participation. Safety laboratory and PK samples will be collected at specified intervals throughout the study as per the Schedule of Evaluations. Subjects will keep a daily diary of solicited systemic symptoms for 3 days after study product administration.

The study will be conducted by the VRC Clinical Trials Program (CTP) at the Vaccine Evaluation Clinic, NIH Clinical Center (NIH CC).

4.1 Study Population

All inclusion and exclusion criteria must be evaluated for eligibility.

4.1.1 Inclusion Criteria

A volunteer must meet all of the following criteria:

1. Able and willing to complete the informed consent process.
2. Available for clinical follow-up through the last study visit.
3. 18 to 60 years of age.
4. In good general health without clinically significant medical history.
5. Willing to have blood samples collected, stored indefinitely, and used for research purposes.
6. Able to provide proof of identity to the satisfaction of the study clinician completing the enrollment process.
7. Physical examination without clinically significant findings within the 84 days prior to enrollment.
8. Have screening laboratory values within 84 days prior to enrollment that meet the following criteria:
    - WBC 2,500-12,000/mm^3

- WBC differential either within institutional normal range or accompanied by the Principal Investigator (PI) or designee approval
- Platelets = 125,000 – 400,000/mm^3
- Hemoglobin within institutional normal range or accompanied by the PI or designee approval
- Creatinine ≤ 1.1 x upper limit of normal (ULN)
- ALT ≤1.25 x ULN
- Negative for human immunodeficiency virus (HIV) infection by a Food and Drug Administration (FDA) approved method of detection
- Negative for Hepatitis B core antibody (HBcAb) and Hepatitis C virus antibody (HCV Ab)

Criteria applicable to women of childbearing potential:

9. If a woman is of reproductive potential and sexually active with a male partner, then she agrees to use an effective means of birth control from the time of study enrollment until the last study visit, or to be monogamous with a partner who has had a vasectomy.
10. Negative human chorionic gonadotropin (β-HCG) pregnancy test (urine or serum) on day of enrollment and product administration.

4.1.2 Exclusion Criteria

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

1. Previous receipt of a licensed or investigational monoclonal antibody or Ebola vaccine.
2. Weight >100 kg.
3. 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.
4. Hypertension that is not well controlled.
5. Woman who is breast-feeding or planning to become pregnant during study participation.
6. Receipt of any investigational study product within 28 days prior to enrollment.
7. 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, psychiatric disorders, heart disease, or cancer.
8. Bleeding disorder diagnosed by a doctor (e.g. factor deficiency, coagulopathy, or platelet disorder requiring special precautions) or significant bruising or bleeding difficulties with IM injections or blood draws.
9. Use of angiotensin-converting enzyme (ACE) inhibitors or other potential nephrotoxins.

4.2 Clinical Procedures and Laboratory Assays

Safety evaluations will include laboratory studies, medical history, and physical assessment by clinicians. The study schedule is provided in Appendix III. Total blood volume drawn from each subject will comply with the NIH CC Guidelines available on the NIH intranet at the following link: http://cc-internal.cc.nih.gov/policies/PDF/M95-9.pdf.

4.2.1 Screening

Screening for this study will be completed through the VRC's screening protocol, VRC 500 (NIH 11-I-0164); no screening evaluations will be performed within this protocol. Volunteers will be recruited through Institutional Review Board (IRB)-approved advertising.

The evaluations and sample collection that will be included in screening are a medical history, physical exam, any laboratory tests needed to confirm eligibility, and pregnancy test for females of reproductive potential. The screening evaluations are outlined in Appendix III. Additional assessments of health may be conducted at screening based on clinical judgment. Only subjects determined to be eligible after screening is completed will be enrolled. Research samples of peripheral blood mononuclear cells (PBMCs), plasma and serum will also be collected. VRC 608 informed consent documents will be reviewed. Counseling related to potential risks of the study product and pregnancy prevention will be performed. An Assessment of Understanding (AoU) will be completed in association with enrollment into VRC 608. Records will be maintained that document the reason(s) why a screened individual was not enrolled.

4.2.2 Enrollment, Study Days and Visit Numbers

Clinicians must discuss the target dates and timing of the study product administration and sample collections before completing each enrollment to help ensure that the subjects can comply with the projected schedule. In this study, enrollment is defined as the assignment of a study identification number and study group schedule in the clinical database. Informed consent must be obtained prior to enrollment. Enrollment 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).

Visit 02 (Day 0) is defined as the day of MAb114 administration. Day 0 is preferably conducted within 14 days after enrollment but may occur up to 28 days after enrollment if needed. This period may be increased with PI approval.

For calculating elapsed days following Day 0, each subsequent calendar date is labeled by the next sequential "Study Day" as shown in the Schedule of Evaluations, Appendix III. 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.

Medical history and Day 0 evaluations prior to the study product administration are the baseline for subsequent safety assessments.

4.2.3 Administration of MAb114

All study product administrations will be completed according to the group assignment. For women of childbearing potential, study product administration may not proceed unless a negative pregnancy test has been obtained. Prior to study product administration, temperature, blood

pressure, heart rate (pulse) and weight will be collected, and a targeted physical examination will be conducted.

In all study groups, the subject will be observed for at least 4 hours following completion of product administration. Following the first product administration for each group, the study team will wait at least 3 days before administering MAb114 to additional subjects within that group.

On Day 0, an IV access will be established in an arm vein using aseptic technique. 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. MAb114 will be diluted with normal saline and infused over a period of approximately 30 minutes; longer infusion times will be permitted. Infusion should continue until the bag is empty. If the subject experiences side effects during the infusion, the rate of infusion may be slowed or stopped to alleviate the symptoms.

Procedures for MAb114 preparation and administration are described in Section 7.

4.2.4 Solicited Adverse Events and Clinical Follow-up

Subjects will be asked to record temperature and systemic symptoms daily for 3 days after the study product administration. Subjects will be trained and encouraged to use the electronic database to record reactogenicity but will have the option to use a paper diary card. When the 3-day diary parameters are recorded directly by the subject into the database, the subject's electronic record will be available to clinicians in real time and will be the source for these data. If concerns arise based on the subject's report of symptoms, clinicians may follow up with additional phone calls during the reactogenicity period as needed. The paper diary will be the source document, if used by the subject. When neither a paper nor electronic diary is available from the subject, the clinician will note the source of reactogenicity information recorded in the study database.

For this study, solicited systemic parameters occurring during the 3 days after receipt of study product will include: unusually tired/feeling unwell, muscles aches, headache, chills, nausea and joint pain. Subjects will also record highest measured temperature daily. Subject diaries are reviewed for accuracy and completeness at follow-up visits and reactogenicity is recorded without an attribution assessment. Clinicians will follow and collect resolution information for any reactogenicity symptoms that are not resolved within 3 days.

Local symptoms will be assessed and recorded by the clinicians. Local reactogenicity parameters will include pain/tenderness, swelling, redness, bruising, and pruritus (itchiness) at the product administration site. Clinicians will assess the study product administration site(s) for local reactogenicity on the day of product administration after completion of the administration and during the scheduled follow-up time points as noted in the Schedule of Evaluations (Appendix III).

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, arthralgia or other clinical concerns may prompt a study visit based on the judgment of a study clinician.

Clinical laboratory assays and clinical evaluations will assess for safety and tolerability at specified intervals post study product administration. Any new or concerning symptoms will be fully assessed to include specialty consultation at the NIH CC as clinically indicated.

4.2.5 Pharmacokinetics

PK samples will be collected as close as reasonably possible to the target timepoints. Because the time of blood collection is critical for PK analysis, the actual time of the phlebotomy will be recorded for all samples. The PK target timepoints are defined in the Schedule of Evaluations (Appendix III).

4.2.6 Schedule of Evaluations

The Schedule of Evaluations (Appendix III) provides details on the study schedule and the permitted visit windows. After enrollment, deviations from the visit windows are discouraged but will be permitted at the discretion of the PI or designee and will be recorded as protocol deviations.

Additional visits and blood draws may be scheduled during the study if needed to assess subject safety or for sample collection in support of immunological testing provided the cumulative blood collection volume complies with NIH CC guidelines. After study completion, subjects may be invited to participate in one of the VRC sample collection protocols (VRC 200 or VRC 900) for follow-up sample collection.

Any evaluation for an adverse event (AE) or possible exacerbation of a pre-existing condition may be scheduled at the study team's discretion as a "protocol-related" evaluation.

4.2.7 Concomitant Medications

Only routine prescription and over the counter medications, and herbal supplements, will be entered in the database at the time of enrollment. Subsequently, concomitant medications associated with an AE that requires expedited reporting or the development of a new chronic condition requiring ongoing medical management will be recorded in the database. Otherwise, concomitant medications taken throughout the study will be recorded in the subject's chart as needed for general medical documentation but will not be recorded in the study database.

4.3 Criteria for Dose Escalation

There are two dose escalation reviews in this study. The PSRT (Section 8.8) will conduct an interim safety data review before the dose escalation may occur. The PSRT must assess the data as showing no significant safety concerns before proceeding with enrollment of each subsequent group.

- The first dose escalation review (from 5 mg/kg IV to 25 mg/kg IV) will occur when all 3 subjects who received the 5 mg/kg IV dose have completed Visit 05, 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 25 mg/kg IV to 50 mg/kg IV) will occur when all 5 subjects who received the 25 mg/kg IV dose have completed Visit 05, the Day 7 safety follow-up visit. The PSRT review will determine whether enrollment into Group 3 may begin.

If there are discontinuations from the study before there are sufficient data to conduct the dose continuation review for a specific group, then extra subjects may be enrolled into that group to obtain the requisite data on at least 3 (Group 1) or 5 (Group 2) subjects. 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 and FDA, if needed, as per study pause criteria (Section 4.5) will occur if indicated by the review. The IRB will be provided with documentation of the safety review process and notification of the dose escalation.

4.4 Criteria for Discontinuing Study Participation

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

1. Subject decides to discontinue participation;
2. Subject develops a medical condition that is a contraindication to continuing study participation;
3. The IND sponsor or regulatory authority stops the study;
4. The PI (or designee) assesses that is it not in the best interest of the subject to continue participation in the study or that the subject's compliance with the study is not sufficient.

4.5 Criteria for Pausing the Study and Resuming the Study

Administration of the study product and new enrollments will be paused by the PI according to the criteria noted below. In the event of a pause, the IND Sponsor Medical Officer (MO) and the PSRT will be promptly notified. Pause criteria are as follows:

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

Plan for Review of Pauses and Resuming Rules:

Study product administration and 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. The reviews to make this decision will occur as follows:

- **Pauses for related SAEs**: The IND Sponsor, with participation by the PI, will conduct the review and make the decision to resume, amend or close the study and will notify the FDA and IRB accordingly.
- **Pauses for Grade 3 or higher related AEs**: The IND Sponsor MO, in consultation with the PI, will conduct the review and make the decision to resume, amend or close the study for the Grade 3 or higher AEs that meet criteria for pausing the study. As part of the pause review, the reviewers will also advise on whether the study needs to be paused again for any subsequent events of the same type. The FDA and the IRB will be notified of Grade 3 or higher pause reviews and of the IND Sponsor's decisions.

5. SAFETY AND ADVERSE EVENT REPORTING

5.1 Adverse Events

An AE is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom, or disease temporally associated with the use of study treatment, whether considered related to the study treatment.

AEs will be graded according to the *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events* (see Appendix IV).

Reporting of all AEs will occur during the period from study product administration at Day 0 through 28 days after study product administration. From Day 28 through completion of study participation, only SAEs and new chronic medical conditions that require ongoing medical management will be recorded as AEs in the study database.

5.2 Serious Adverse Events

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

5.3 Adverse Event Reporting to the IND Sponsor

AEs that meet SAE Reporting Requirements 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
- results in persistent or significant disability/incapacity
- requires unplanned inpatient hospitalization or prolongation of existing hospitalization
- is a congenital anomaly/birth defect in the offspring of a study subject
- is an important medical event that may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above.

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

An investigator will communicate an initial SAE report within 24 hours of site awareness of occurrence to the IND sponsor by email to the VRC Protocol Operations Office (see Appendix II).

A written report by the investigator should be submitted to the IND Sponsor within 3 working days. 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.

5.3.1 IND Sponsor Reporting to the FDA

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

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

All SUSARs, as determined by the IND Sponsor, will be reported to the FDA as IND Safety Reports and IND Safety Reports will 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.

5.4 Reporting to the Institutional Review Board

5.4.1 Unanticipated Problem (UP) Definition

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

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

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

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

5.4.2 Protocol Deviation Definition

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

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

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

5.4.3 Non-Compliance Definition

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

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

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

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

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

5.4.4 Expedited Reporting to the IRB

The following will be reported to the NIAID IRB within 7 calendar days of investigator awareness:

- Serious and non-serious UP
- Deaths
- Serious protocol deviations
- Serious or continuing non-compliance
- SAEs that are possibly, probably, or definitely related to the research regardless of expectedness

The following waiver applies to reporting anticipated protocol deviations and expected UPnonAEs: Anticipated deviations in the conduct of the protocol will not be reported to the IRB unless they occur at a rate greater than anticipated by the study team. Expected AEs will not be reported to the IRB unless they occur at a rate greater than that known to occur in healthy adults. If the rate of these events exceeds the rate expected by the study team, the events will be classified and reported as though they are unanticipated problems.

5.4.5 Annual Reporting to the IRB

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

- Serious and non-serious UPs
- Expected SAEs that are possibly, probably, or definitely related to the research
- SAEs that are not related to the research
- All AEs, except expected AEs granted a waiver of reporting
- Serious and non-serious Protocol Deviations
- Serious, continuing, and minor non-compliance
- Any trends or events which in the opinion of the investigator should be reported

6. STATISTICAL CONSIDERATIONS

6.1 Overview

This is a Phase I, open-label, dose-escalation study of the safety and pharmacokinetics of a human monoclonal antibody, MAb114, administered intravenously to healthy adults.

6.2 Objectives

The primary objectives of the study are to evaluate the safety and tolerability of MAb114, to evaluate the pharmacokinetics of MAb114, and to estimate the half-life of MAb114 in serum.

6.3 Size and Accrual

6.3.1 Sample Size Considerations

This study is primarily descriptive. For safety analysis, the goal is to identify safety concerns associated with different MAb114 dosages. There may be as few as 3 to 10 subjects in a group; therefore, this section considers group sizes of n=3, 5 and 10.

The ability to identify serious adverse experiences is best expressed by the maximum true rate of SAE that would unlikely be observed and the minimum true SAE rate that would very likely be observed. Within a group of size n=3, there is an 80% chance of observing at least 1 event if the true rate is no less than 0.42 and a 90% chance of observing no event if the true rate is no bigger than 0.035. Within a group of size n=10, there is at least an 80% chance of observing at least 1 event if the true rate is no less than 0.15 and at least a 90% chance of observing no event if the true rate is no bigger than 0.1.

Probabilities of observing 0 or more than 1 event are presented in **Table 4** for a range of possible true event rates. These calculations provide a complete picture of the sensitivity of this study design to identify potential safety problems with the study agent. For example, within the group of size n=3, if the true event rate is 0.1, then there is a 73% probability of observing no event and a 2.8% probability of observing more than 1 event; while, within the group of size n=10, if the true event rate is 0.1, then there is a 35% probability of observing no event and an 26% probability of observing more than 1 event.

Table 4: Probability of Event for Different Scenarios

True event rate	Within a group (n=3)		Within a group (n=5)		Within a group (n=10)	
	Pr (0 event observed)	Pr (more than 1 event observed)	Pr (0 event observed)	Pr (more than 1 event observed)	Pr (0 event observed)	Pr (more than 1 event observed)
0.05	0.857	0.007	0.774	0.023	0.599	0.086
0.1	0.729	0.028	0.590	0.081	0.349	0.264
0.2	0.512	0.104	0.328	0.263	0.107	0.624
0.3	0.343	0.216	0.168	0.472	0.028	0.851
0.4	0.216	0.352	0.078	0.663	0.006	0.954

Table 5 gives the upper and lower bounds for 95% exact binomial confidence intervals (CIs) for all possible number of observed events within a group. Within the group of size n=3, if no subjects experience the event, the 95% exact 2-sided CI for the true rate has an upper bound of 0.708; if all subjects experience the event, the 95% exact 2-sided CI for the true rate has a lower bound of 0.292. Within the group of size n=5, if no subjects experience the event, the 95% exact 2-sided CI for the true rate has upper bound of 0.522; if all subjects experience the event, the 95% exact 2-sided CI for the true rate has a lower bound of 0.478. Within the group of size n=10, if no subjects experience the event, the 95% exact 2-sided CI for the true rate has upper bound of 0.308; if all subjects experience the event, the 95% exact 2-sided CI for the true rate has a lower bound of 0.692.

Table 5: 95% Confidence Intervals of the True Rate for All Possible Number of Observed Events Within a Group

Within a group (n=3)		Within a group (n=5)		Within a group (n=10)	
Observed rate	**95% CI**	**Observed rate**	**95% CI**	**Observed rate**	**95% CI**
0/3	0, 0.708	0/5	0, 0.522	0/10	0, 0.308
1/3	0.008, 0.906	1/5	0.005, 0.716	1/10	0.002, 0.445
2/3	0.94, 0.992	2/5	0.053, 0.853	2/10	0.025, 0.566
3/3	0.292, 1	3/5	0.147, 0.947	3/10	0.067, 0.652
		4/5	0.284, 0.995	4/10	0.122, 0.738
		5/5	0.478, 1	5/10	0.187, 0.813
				6/10	0.262, 0.878
				7/10	0.348, 0.933
				8/10	0.444, 0.975
				9/10	0.555, 0.997
				10/10	0.692, 1

Tables 4 and 5 also apply to the secondary and exploratory objectives.

6.4 Statistical Analysis

6.4.1 Analysis Variables

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

6.4.2 Baseline Demographics

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

6.4.3 Safety Analysis

Summaries of the number and percentage of subjects experiencing any AE or reactogenicity will be tallied by group and presented along with exact 95% confidence intervals for the proportion.

Solicited Adverse Events:

Solicited AE data is collected after each dose administered in this study. The number and percentage of subjects experiencing each type of solicited sign or symptom will be tabulated by severity. For a given sign or symptom, each subject's solicited AEs will be counted once under the maximum severity for all assessments.

Adverse Events:

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

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

Local laboratory values:

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

6.4.4 Tolerability Evaluation

The tolerability of the medical product represents the degree to which overt adverse effects can be tolerated by the subject [23]. VRC 608 is the first trial of MAb114 in healthy adults. The tolerability evaluation will be mostly descriptive by nature and consist of solicited AEs that occur during the 3 days following MAb114 administration and reasons for any withdrawal or discontinuation based upon subject discomfort. This early assessment of tolerability of MAb114 will inform which parameters should be solicited or routinely assessed to further characterize the tolerability profile in a larger number of subjects.

6.4.5 Pharmacokinetics Analysis

Blood samples for PK evaluations will be collected at timepoints per the Schedule of Evaluations.

Individual Subject PK Analysis: A non-compartmental PK analysis will be performed using Phoenix (Centara) or a similar program on the MAb114 concentration data generated from each subject. Calculated PK parameters for all groups will include: area-under-the-curve (AUC), maximum concentration (Cmax), time to Cmax (Tmax), clearance (CL), volume of distribution (Vdz), terminal elimination rate constant (λz) and the terminal half-life ($T_{1/2}$). Cmax and Tmax will be taken directly from the observed concentration-time data. The terminal slope, λz, will be determined from the log-linear portion of the curve and the $T_{1/2}$ calculated as $0.693/\lambda z$. $AUC_{0\text{-}Clast}$ will be determined using the linear trapezoidal method, where C_{last} is the concentration at 24 weeks after the dose. If the final sample (C_{last}) has measurable MAb114 concentrations, the remaining AUC after the final concentration ($AUC_{Clast\text{-}inf}$) will be estimated as $Clast/\lambda z$. Data will be summarized by dose group.

Population PK Analyses: Population PK analyses will be performed on the MAb114 PK data following IV administration to determine compartmental PK parameters using the program NONMEM. One and two compartment PK models will be assessed. Based on prior PK studies of antibodies, it is anticipated that a two-compartment model will adequately characterize the data. The population analysis will generate estimates for initial and final volumes of distribution (Vd_1 and Vd_2), inter-compartmental clearance (Q), CL and bioavailability (F). Volume of distribution at steady-state (Vd_{ss}) will be calculated as the sum of $Vd_1 + Vd_2$. Given the small subject numbers, the population PK analysis will not include an exploratory covariate analysis to assess clinical

factors as fixed effects associated with MAb114 PK parameters with the exception of dose (5 vs 25 vs 50 mg/kg) as fixed effects on CL and Vd_{ss}. The terminal half-life, $t_{1/2\beta}$ will be determined from CL, Vd_1, Vd_2 and Q. Final model selection will be based on changes in the objective function and graphically by goodness of fit plots. The final population model will be assessed using bootstrap analysis. MAb114 dosing strategies and their ability to achieve and maintain target MAb114 concentrations will be performed using the final population PK model and Monte Carlo simulations with at least 5000 replicates.

6.4.6 Interim Analyses

Preliminary PK analyses may be performed once per dose level as the data for each dose level is obtained. This will be used to inform decisions about the dose levels to be administered in studies that may begin while VRC 608 is still in progress.

7. PHARMACY PROCEDURES

The study groups and study product dosing schedule are shown in **Table 3**. Refer to the IB for further information about the investigational study product and administration regimen.

7.1 Study Product and Administration Regimen

The study includes an investigational monoclonal antibody described as follows:

- VRC-EBOMAB092-00-AB (MAb114)

In this study, the amount of antibody needed for dosing is based on subject weight and treatment group assigned. In calculating the dose to administer, it should be assumed that the concentration of reconstituted MAb114 is 50 mg/mL, and that a volume of at least 8 mL can be withdrawn from a vial.

For example, if a subject is 80 kg, the volumes for clinical dosing per infusion would be as follows:

- If an 80 kg subject enrolled in Group 1 (5 mg/kg), 400 mg (8 mL) should be administered
- If an 80 kg subject enrolled in Group 2 (25 mg/kg), 2000 mg (40 mL) should be administered
- If an 80 kg subject enrolled in Group 3 (50 mg/kg), 4000 mg (80 mL) should be administered

Preparation of MAb114 for IV administration will require 0.9% sodium chloride, USP (normal saline). For all groups, normal saline (100 mL preferred) and weight-based amount of reconstituted MAb114 will be added to a sterile empty bag (250 mL preferred).

7.2 Study Product Storage

The product label designates the long-term storage temperature as 2-8°C. The site pharmacist must promptly report any storage temperature excursions to the IND sponsor's authorized representative (Appendix II). The affected product must be quarantined in a separate area. The IND Sponsor's authorized representative will notify the site pharmacist if continued clinical use of the product is acceptable.

7.3 Preparation of Study Product for Administration

This section describes how the site pharmacist will prepare the study product for administration and how the clinician will administer the product.

Preparation is to be done in a limited access, biological safety cabinet with laminar flow using aseptic technique. During preparation, the pharmacist should assure that only the required vials are present in the preparation unit, and medication labels are strictly segregated to avoid mix-ups.

The following instructions apply to preparing the product for infusion:

1. Calculate the total amount of MAb114 (mg) needed based on the subject's weight and assigned dose level.
2. Remove vial(s) from storage and equilibrate to room temperature for at least 20 minutes
3. Add 7.7 mL of SWFI to each vial
4. Gently mix the vial by swirling, stopping every 30 seconds to let the vial sit on the counter for 10 seconds, until reconstitution is complete. Reconstituted product should be a clear, light yellow liquid, essentially free of visible particles. It may take up to 30 minutes to achieve a completely clear (particle free) solution. If particles are still observed in a vial, the vial should not be used for product administration.

Reconstituted or diluted drug product will be maintained for no more than 4 hours at room temperature or 24 hours at 2°-8°C prior to administration.

More information on product preparation can be found in the IB.

It is expected that each vial will be used for the 8 mL withdrawal volume (400 mg of MAb114); however, more may be withdrawn if it is possible to do so. For each IV infusion order, the subject's weight and dose level will be included in the pharmacy order.

To prepare an IV infusion, the pharmacist will fill an empty sterile bag (250 mL preferred) with normal saline (100 mL preferred), calculate the total amount of MAb114 (mg) needed, reconstitute the minimum number of vials needed to obtain the full dose and add the calculated total mg needed to the sterile bag filled with normal saline (100 mL preferred) using good pharmacy practices to maintain sterility.

An in-line filter infusion set must be used for all IV product administrations. The pharmacist should add the in-line filter to the tubing and prime the set prior to delivery to the clinical setting. In-line filters must comply with the following specifications: 1.2 micron PES (polyether sulfone) filter membrane, DEHP-free, latex-free.

The IV bag prepared by the pharmacy will include the total amount (mg) of MAb114 added to normal saline in an empty sterile bag, and an in-line filter infusion set.

Before beginning the IV administration, the clinician responsible for administration and another clinician will each check the bag label and verify the identifier, the dosage level, that the total amount of product to be administered is correct based on the subject's weight, and that the filter is in place.

The investigational study product solution will typically be administered by IV infusion for approximately 30 minutes, based on factors such as subject tolerance, using a volumetric pump. Longer infusion times will be allowed if clinically warranted.

7.4 Labeling of Study Product

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

7.5 Study Product Accountability

The study pharmacist will be responsible for maintaining an accurate record of the codes, inventory, and an accountability record of study product 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 after use. 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 products. 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 study will be conducted in compliance with the protocol, International Council for Harmonisation's Good Clinical Practice (ICH-GCP) guidance, and all applicable regulatory requirements.

8.1 Informed Consent

The study informed consent form (ICF) is provided in Appendix I. It describes the study product to be used and all aspects involved in protocol participation.

The PI or designee is responsible for obtaining written informed consent from each subject after adequate explanation of the aims, methods, anticipated risks and benefits of the study and before any protocol-specific procedures are conducted or the 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. The ICF will be signed and personally dated by the subject, the person who conducted the informed consent discussion, and a witness. The original signed ICF will be retained in the medical chart and a copy will be provided to the subject.

8.2 Risks and Benefits

8.2.1 Risks

MAb114: There is no prior human experience with administration of MAb114.

MAbs: 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 murine MAbs that would have

a risk of human anti-mouse antibodies [24]. In this regard, because MAb114 is targeted to a viral 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 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 [24]; however, this is not expected to be a risk for a MAb targeted to a viral antigen.

Published experience with human MAbs directed against the 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) [25]. Most infusion-related events occur within the first 24 hours after beginning administration. 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 murine MAb [24]. CRS reactions most commonly occur within the first few hours of beginning infusion 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 [26]. Supportive treatment may also be indicated for some signs and symptoms. Delayed allergic reactions to a MAb may include a serum sickness type of reaction, which is characterized by urticaria, fever, lymph node enlargement, and joint pains. Symptoms may not appear until several days after the exposure to the MAb. This type of reaction is noted to be more common with chimeric types of MAb [24]. 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 and bruising and, infrequently, may cause 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 Day 0 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.

8.2.2 Benefits

There are no direct benefits to subjects from study participation. Others may benefit from knowledge gained in this study that may aid in the development of EVD prevention or therapeutic methods.

8.3 Institutional Review Board

A copy of the protocol, ICF, other written subject information, and any advertising material will be submitted to the IRB for written approval prior to implementation.

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 unanticipated problems, non-compliance, deviations from the protocol, and SAEs per IRB policy.

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

8.4 Subject Confidentiality

The investigator must ensure that no information identifying the subject will be released to any unauthorized party. Individual identifying information will not be included in any reports. Subjects will be identified only by coded numbers. All records will be kept confidential to the extent provided by federal, state and local law. Medical records are made available for review when required by the FDA or other authorized users, such as the study product manufacturer, only under the guidelines set by the Federal Privacy Act. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform the subjects that the above-named representatives will review their study-related records without violating the confidentiality of the subjects.

8.5 Plan for Use and Storage of Biological Samples

The plan for use and storage of biological samples from this protocol is as outlined as follows.

8.5.1 Use of Samples, Specimens and Data

Samples, specimens and data collected under this protocol may be used to conduct protocol-related safety and immunology evaluations, exploratory laboratory evaluations related to the biological target of the study product, exploratory laboratory evaluations related to vaccine or infectious disease research in general and for research assay validation. Genetic testing may be performed in accordance with the genetic testing information that is included in the study informed consent.

8.5.2 Storage and Tracking of Blood Samples and Other Specimens

All research samples use coded labels that only the VRC Clinic can link to the subject. Samples are stored at the VITL, Gaithersburg, MD or VRC Laboratories in Building 40, 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 or GlobalTrace).

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

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

At the time of protocol termination, samples will remain in the VITL facility or VRC laboratories or, after IRB approval, 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.

8.5.4 Loss or Destruction of Samples, Specimens or Data

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

8.6 Subject Identification and Enrollment

All study activities will be carried out at the NIH CC. Study subjects will be recruited through on-site and off-site advertising done through the screening protocol, VRC 500 (NCT 01375530) (https://clinicaltrials.gov/ct2/show/NCT01375530?term=VRC+500&rank=1). Effort will be made to include women and minorities in proportions similar to that of the community from which they are recruited and will be limited to persons at least 18 years of age and no older than 60 years of age at enrollment.

8.6.1 Participation of 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.

8.6.2 Participation of NIH Employees

NIH employees and members of their immediate families may participate in this protocol. The VRC clinic will follow the NIH Guidelines for the Inclusion of Employees in NIH Research Studies.

The NIH information sheet "NIH Information Sheet on Employee Research Participation." regarding 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 NIH CC and NIAID policies. Neither participation nor refusal to participate will have an effect, either beneficial or adverse, on the subject's employment or work situation. 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 provided 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 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 product administration and PK blood draws on the same day will be $375. The compensation will be $175 for scheduled visits that include blood draws, $75 for clinic visits that do not include a blood draw or procedure, and $25 for timely completion of the electronic diary.

8.8 Safety Monitoring

Close cooperation between the designated members of the Protocol Team will occur to evaluate and respond to individual AEs in a timely manner. The designated VRC Safety Officer will conduct a daily safety review of clinical data per VRC Standard Operating Procedures. The PSRT, comprised of the PI, Associate Investigators, Study Coordinator, Protocol Specialists, other Study Clinicians, and MO will review the summary study safety data reports on a weekly basis through 4 weeks after the last subject receives the study product and will continue to monitor the safety data reports monthly through completion of the last study visit.

9. ADMINISTRATIVE AND LEGAL OBLIGATIONS

9.1 Protocol Amendments and Study Termination

Protocol amendments may be made only with the prior approval from the IND Sponsor. Agreement from the PI and MO must be obtained for all amendments to the protocol and the informed consent document. All study amendments will be submitted to the IRB for approval.

The IND Sponsor, NIAID IRB, OHRP, study PI, and FDA reserve the right to terminate the study at any time. 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 maintain a list of appropriately qualified persons to whom trial duties have been delegated.

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

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 VRC, IRB, FDA, and/or applicable regulatory authorities. Elements include:

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

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 or refusal (21 CFR 312.62). 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 Study Monitoring, Data Collection and Data Sharing

9.3.1 Study Monitoring

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

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

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

9.3.2 Data Collection

Clinical research data will be collected in a secure electronic data management system through a contract research organization, The EMMES Corporation (Emmes) in Rockville, MD. Extracted data without patient identifiers will be sent to the PSRT for safety review and to the Protocol Statistician for statistical analysis.

9.3.3 Data Sharing Plan

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

9.4 Language

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

9.5 Policy Regarding Research-Related Injuries

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

10. REFERENCES

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Appendix I: Study Informed Consent Form

Text of the IC is included in the NIH CC Informed Consent Template and provided as a separate document.

Appendix II: Contact Information

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Sharon Adams
Laboratory Services Section
NIH, Clinical Center Department of Transfusion Medicine (CC/DTM)
Building 10 Room 1C711
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Research Immunology Central Laboratory:
Vaccine Immunology Testing Laboratory (VITL)
9 West Watkins Mill Road, Suite 150
Gaithersburg, MD 20878

Product Manufacturer:
Cook Pharmica LLC d.b.a. Catalent Indiana, LLC (Bloomington, IN) contracted by
MedImmune, LLC
Gaithersburg, MD

Study Site: National Institutes of Health Clinical Center Vaccine Evaluation Clinic 5NES, Building 10, Bethesda, MD 20892 **VRC Protocol Operations:** Eugeania Burch, MPH, 301-761-7836 Nina Berkowitz, MPH, 240-747-7940 Galina Yamshchikov, MS, 301-761-7056 Olga Vasilenko, MS, 301-761-7171 Iris Pittman, BA, CCRP, 301-761-6994 Maria C. Burgos Florez, MS, 301-761-7338 Ro Shauna S. Rothwell, PhD, 301-761-7465 Somia Hickman, PhD, 301-761-7884 Lam Le, MBA, CCRP, 301-761-7656 Olga Trofymenko, MD, 240-292-0684	**Pharmacy:** Investigational Drug Control Unit (CC-PHAR IDCU)**,** CC-PHARIDCU@mail.nih.gov, 301-496-1031 Investigational Drug Management and Research Section Clinical Center, Building 10/1C230 Bethesda, MD 20892 **VRC Production Program:** Frank J. Arnold, PhD, 240-669-5171 KC Cheng, PhD, 301-761-7326 Judy Stein, MPH, MBA, 734-761-3221 **VRC Office of Regulatory Science:** *Carolyn Laurencot, PhD, 301-761-7855 (*sponsor authorized representative for this IND) Michelle Conan-Cibotti, PhD, RAC, 240-292-4938 Sandra I. Vazquez, MS, RAC., 301-761-6554 Tatiana Beresnev, MD, MSHS, 301-761-7062

Appendix III: Schedule of Evaluations

VRC 608 Schedule of Evaluations											
		Visit Number	01R	02	02A	02B	02C	02D	03	04	05
		Time After Day 0 Infusion		Pre	EOI	1hr	3hr	6hr	24hr	48hr	Wk1
		[1]Day of Study	-28 to 0	D0	D0	D0	D0	D0	D1	D2	D7
Study Procedures	**Tube**	**[2]Screen -84 to 0**	**Enroll**								
VRC 500 Screening Consent		X									
VRC 608 Assessment of Understanding; Consent			X								
[3] Physical exam		X	X	X	X				X	X	X
[4] Medical history		X	X	X					X	X	X
[5] Concomitant Medications		X	X	X					X	X	X
[6] Study Product Administration				X							
[7] Administration Site Evaluation									X	X	X
[8] Reactogenicity Diary				X					X	X	X
[9] Pregnancy prevention counseling		X	X	X							
Clinical Labs											
CBC with differential	EDTA	3		3						3	3
CMP	GLT	4		4							
ALT, creatinine	GLT									4	4
[9] Pregnancy test: urine or serum		X	X	X							
HIV EIA	SST	4									
HBcAb	SST	4									
HCV Ab	SST	4									
Research Samples											
Timed PK samples	SST			8	8	8	8	8	8	8	8
PBMC and plasma	EDTA		20					20		10	20
Serum	SST		24†							8	16
Daily Volume (mL)		**19**	**44**	**15**	**8**	**8**	**8**	**28**	**8**	**33**	**51**
Cumulative Volume (mL)		**19**	**63**	**78**	**86**	**94**	**102**	**130**	**138**	**171**	**222**

Visit Windows:

Screening: Evaluations for eligibility must be completed with 84 days of enrollment as noted in Section 4.1.

Visit 01R and Day 0: Visit 01R may be done on the same day as Day 0. Visit 01R = day of enrollment. Day 0 = day of product administration. Day 0 is preferably scheduled within 14 days after enrollment at Visit 01R, but may be scheduled up to 28 days after enrollment. Day 0 evaluations prior to MAb114 administration are the baseline for assessing subsequent AEs.

EOI: End of Infusion blood draw visits, defined by minutes or hours after an infusion, are relative to the exact time of the end of infusion (EOI). The exact time of start (T0), EOI and each PK draw are recorded to ensure accurate PK analysis. **It is preferable to draw PKs as close to target time as possible.**

Visit 02A: up to 10 minutes post EOI Visits 02B, 02C: ± 10 minutes Visit 02D: -2 hours Visits 03, 04: ± 6 hours Visit 05: ± 2 days

Footnotes:

[1] Day 0=day of product administration. Day 0 is preferably scheduled within 14 days after enrollment at Visit 01R, but may be scheduled up to 28 days after enrollment.

[2] Screening: All screening evaluations including laboratory tests, medical history and complete physical exam must be completed within 84 days of enrollment.

[3] Physical exam: Screening includes complete physical exam with vital signs, height and weight. Day 0 physical exam includes vital signs (blood pressure, temperature and pulse) and weight (used for ordering the study product which is based on a "mg/kg" dose). At other visits if medically indicated, a targeted exam is performed. Otherwise only blood pressure, pulse and temperature are required.

[4] Medical history: Screening, 01R and Day 0 evaluations include a complete medical history to evaluate eligibility criteria as defined in Section 4.1. At other visits, an interim medical history will be completed.

[5] Concomitant medications: Concomitant medications must be entered in the database at enrollment and updated as required in Section 4.2.7.

[6] Study product administration: Group 1 subjects will receive a single infusion of 5 mg/kg IV, Group 2 subjects will receive a single infusion of 25 mg/kg IV, and Group 3 subjects will receive a single infusion of 50 mg/kg IV.

[7] Administration Site Evaluation: Clinicians will assess the product administration site on Days 1, 2 and 7 and record any findings in the database. Any signs or symptoms unresolved by Day 7 should continue to be evaluated until resolved.

[8] Reactogenicity Diary: Subjects will begin to record 3-day systemic reactogenicity after study product administration as noted in Section 4.2.4. Clinicians will review with the subject at a minimum on Days 1, 2 and 7. If any reported reactogenicity is unresolved by Day 3, it will continue to be reviewed with the subject until resolved which may require an interim phone contact. Data from the diary will be recorded in the database as noted in Section 4.2.4.

[9] Pregnancy test and pregnancy prevention counseling are required at visits as indicated for women of reproductive potential. Negative pregnancy test results must be confirmed for women of reproductive potential prior to MAb114 administration.

[†]Anti-drug antibodies (ADA) will be assessed from serum samples taken at baseline, four weeks post-infusion, and 24 weeks post-infusion at the final protocol visit. Banked serum from any study visit may also be used for ADA assessment as indicated from observations in an individual subject prompting suspicion of ADA development, such as a precipitous drop in PK levels.

VRC 608 Schedule of Evaluations (continued)												
Visit Number		06	07	08	09	10	11	12	13	14	15	16
Week of Study		Wk2	Wk3	Wk4	Wk5	Wk6	Wk7	Wk8	Wk12	Wk16	Wk20	Wk24
Day of Study		D14	D21	D28	D35	D42	D49	D56	D84	D112	D140	D168
Study Procedures	**Tube**											
[1]Physical exam		X	X	X	X	X	X	X	X	X	X	X
Interim medical history		X	X	X	X	X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X
[2]Pregnancy prevention counseling								X	X	X		
Clinical Labs												
CBC with differential	EDTA	3		3				3	3			
CMP	GLT	4										
ALT, creatinine	GLT			4				4				
[2]Pregnancy test: urine or serum								X	X	X		X
[3]HLA typing	EDTA			20								
Research Samples												
[4]PK samples	SST	8	8	8	8	8	8	8	8	8	8	8
PBMC and plasma	EDTA	20		20	20			20	20			20
Serum	SST	24	24	24[†]	16			24	24			24[†]
Daily Volume (mL)		**59**	**32**	**79**	**44**	**8**	**8**	**59**	**55**	**8**	**8**	**52**
Cumulative Volume (mL)		**281**	**313**	**392**	**436**	**444**	**452**	**511**	**566**	**574**	**582**	**634**

Visit Windows:

Visits 06 – 12: ± 2 days Visits 13 – 16: ± 7 days

Footnotes:

[1] Physical exam: If medically indicated, a targeted exam is performed. Otherwise only blood pressure, pulse and temperature are required.

[2] Pregnancy test and pregnancy prevention counseling are required at visits as indicated for women of reproductive potential.

[3] Human leukocyte antigen (HLA) type blood sample: If the HLA type within 2 years is not available in the medical record, a blood sample will be collected once. HLA type may also be obtained from a frozen sample.

[4] PK samples: PK draws may be cancelled at Visits 15 and 16 if results from Visit 14 are available and show no detectable MAb114, however these visits will still be required.

[†] ADA assessed from serum samples as indicated. Banked serum from any study visit may also be used for ADA assessment.

Appendix IV: Table For Grading Severity Of Adverse Events

The U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1. [July 2017] will be used in this study. The table is available at the following link: https://rsc.tech-res.com/docs/default-source/safety/daidsgradingcorrecetedv21.pdf

The Table will be used as posted at the link above with the following exemptions:

- Weight loss will be recorded as an adverse event 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.
- Subclinical CMP results for sodium, potassium, chloride, bicarbonate, BUN, and glucose will not be considered an AE unless grade 2 or greater.
- 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.