Protocol Title: VRC 615: A Phase I, Open-Label, Dose-Escalation Study of the Safety and Pharmacokinetics of a Human Monoclonal Antibody, VRC-HIVMAB0115-00-AB (VRC01.23LS), Administered Intravenously or Subcutaneously to Healthy Adults.

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Documents:

- IRB-approved Protocol (v3.0 October 16, 2023) – Statistical Analysis Considerations located in Section 6 of the Protocol

Version 3.0
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VACCINE RESEARCH CENTER

Protocol VRC 615
NIH 000889

A PHASE I, OPEN-LABEL, DOSE-ESCALATION STUDY OF THE SAFETY AND PHARMACOKINETICS OF A HUMAN MONOCLONAL ANTIBODY, VRC-HIVMAB0115-00-AB (VRC01.23LS), ADMINISTERED INTRAVENOUSLY OR SUBCUTANEOUSLY TO HEALTHY ADULTS

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

Clinical Trial Sponsored by:
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ABBREVIATIONS

Abbreviation	Term
ADA	anti-drug antibody
ADL	activities of daily living
AE	adverse event
AIDS	Acquired Immunodeficiency Syndrome
ALT	alanine aminotransferase
AoU	Assessment of Understanding
ART	antiretroviral therapy
AST	aspartate aminotransferase
AUC	area under the curve
bnAb	broadly-neutralizing antibody
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practice
CL	clearance
Cmax	maximum concentration
CRS	cytokine release syndrome
DP	drug product
DS	drug substance
ECL	electrochemiluminescence
ELISA	enzyme-linked immunosorbent assay
EOI	end of infusion; end of injection
F	bioavailability
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLT	Light green lithium heparin tube
GLP	Good Laboratory Practice
HA	hyaluronan
HCL	hydrochloric acid
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
IgG1	Immunoglobulin G1

Abbreviation	Term
IND	investigational new drug application
IP	investigational product
IRB	Institutional Review Board
IV	intravenous
kg	kilogram
LIMS	Laboratory Information Management System
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
mcg	microgram
mg	milligram
mL	milliliter
mM, mmol	millimole
MO	medical officer
MSD	Meso Scale Discovery
NHP	Non-human primate
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NIH CC	National Institutes of Health Clinical Center
OHRP	Office for Human Research Protections
PBS	phosphate buffered saline
PCR	polymerase chain reaction
PES	polyethersulfone
PI	Principal Investigator
PII	Personal Identifiable Information
PK	pharmacokinetic
PSRT	Protocol Safety Review Team
PT	preferred term
Q	Inter-compartmental clearance
QA	quality assurance
SAE	serious adverse event
SC	subcutaneous
SHIV	simian-human immunodeficiency virus
SOC	system organ class
SOE	Schedule of Evaluation
SST	Serum separator tube
SUSAR	serious and unexpected suspected adverse reaction

Abbreviation	Term
$T_{½}$	half-life
TCR	tissue cross reactivity
Tmax	time of maximal concentration (Cmax)
ULN	upper limit of normal
UNAIDS	Joint United Nations Programme on HIV/AIDS
UP	unanticipated problem
USP	United States Pharmacopeia
Vd	volume of distribution
VEC	Vaccine Evaluation Clinic
VIP	Vaccine Immunology Program
VRC	Vaccine Research Center
WBC	white blood cell
β-HCG	human chorionic gonadotropin
λz	terminal slope of concentration vs time profile

PRINCIPAL INVESTIGATOR PROTOCOL SIGNATURE PAGE

VRC 615: A Phase I, Open-Label, Dose-Escalation Study of the Safety and Pharmacokinetics of a Human Monoclonal Antibody, VRC-HIVMAB0115-00-AB (VRC01.23LS), Administered Intravenously or Subcutaneously to Healthy Adults

I, the Principal Investigator for the study site indicated above, 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 Council for 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.

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, for at least 2 years following submission of a marketing application to FDA (21 CFR 312.62). 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.

Lesia K. Dropulic, M.D	NIH-Clinical Center Vaccine Evaluation Clinic
Name/Title of Principal Investigator	Study Site Name
Signature of Principal Investigator	Date

PRÉCIS

VRC 615: A Phase I, Open-Label, Dose-Escalation Study of the Safety and Pharmacokinetics of a Human Monoclonal Antibody, VRC-HIVMAB0115-00-AB (VRC01.23LS), Administered Intravenously or Subcutaneously to Healthy Adults.

Study Design: This first-in-human, open-label study will evaluate VRC01.23LS (VRC-HIVMAB0115-00-AB) in a dose-escalation design to examine safety, tolerability, dose, and pharmacokinetics (PK) in healthy adults. The primary hypothesis is that subcutaneous (SC) and intravenous (IV) administrations of VRC01.23LS will be safe and well-tolerated in healthy adults. A secondary hypothesis is that VRC01.23LS will be detectable in human sera with a definable half-life.

Study Products: The VRC01.23LS broadly neutralizing monoclonal antibody (bnAb) targets the CD4 binding site in the HIV-1 envelope, is human in origin, and contains two amino acid modifications within the C-terminus of the heavy chain constant region designed to improve the antibody half-life *in vivo*. VRC01.23LS was developed by the VRC/NIAID/NIH and manufactured under cGMP regulations at the VRC Pilot Plant operated under contract by the Vaccine Clinical Materials Program (VCMP), Leidos Biomedical Research, Inc., Frederick. MD.

Subjects: Healthy adults, 18-60 years of age

Study Plan: This open-label study will include 6 groups to evaluate VRC01.23LS administered alone or by repeat dosing as shown below in the Study Schema. Enrollment will begin with the 5 mg/kg dose groups, and enrollment for subsequent dose groups will proceed after dose-escalation safety reviews. Assessment of safety will include solicited reactogenicity, clinical observation, and monitoring of hematological and chemical parameters at clinical visits throughout the study.

VRC 615 Study Schema

Group	Subjects	VRC01.23LS Dose and Route	Dosing Schedule		
			Day 0	Week 12	Week 24
1	3	5 mg/kg IV	X		
2	3	5 mg/kg SC	X		
3	3	20 mg/kg IV	X		
4	3	40 mg/kg IV	X		
5	5	5 mg/kg SC	X	X	X
6	5	20 mg/kg IV	X	X	X
Total	22*	*Enrollment up to a total of 40 subjects is permitted if additional subjects are necessary for safety or PK evaluations.			

Study Duration: Study participation will be approximately 24 weeks after the last product administration.

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council for 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(s) 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(s) will be IRB-approved; an IRB 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

The human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) has remained a major global public health problem since the discovery of the virus in 1983. Reports by the Joint United Nations Programme on HIV/AIDS (UNAIDS) estimate that since 2021 79.3 million people have been infected with HIV since the start of the epidemic, contributing to 36.3 million deaths from AIDS-related illnesses[1]. Despite these statistics, global incidences of new HIV infections have actually declined from peak rates in the mid-1990s; a reduction attributed in part to increased availability of antiretroviral therapy (ART) and the effective execution of prevention/treatment programs such as those that target mother-to-child transmission. Unfortunately, HIV infection is extremely complex and none of the current therapeutic or prophylactic regimens can completely prevent or cure an infection or induce a full recovery of the host immune system. The National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH) is committed to the development of safe, effective methods to prevent and treat HIV infection and AIDS worldwide. In this regard, the Vaccine Research Center (VRC), NIAID and Division of AIDS (DAIDS), NIAID, are collaborating to evaluate the potential clinical uses of HIV-specific broadly neutralizing human monoclonal antibodies (mAb) [2-4]. Thus, novel prevention and cure strategies are being investigated.

In 2018, ibalizumab, which is a CD4-directed post attachment HIV-1 inhibitor, became the first licensed monoclonal antibody therapy indicated for heavily treatment-experienced adults with multi-drug resistant HIV-1 infection failing their current antiretroviral regimen [5]. The licensure of ibalizumab was the culmination of extensive studies over the previous two decades. Efforts to develop effective mAbs against HIV itself have resulted in scientific discoveries and innovations in the first twenty years of the 21st century that include sera screening strategies, pseudovirus neutralization assay development [6-8], and single B-cell isolation and screening techniques [2, 9-11], enabling identification and evaluation of mAbs against HIV-1 in clinical trials [12]; however, to date, an anti-HIV mAb effective for the prevention and/or treatment of HIV-1 infection has yet to be approved.

In 2010, the VRC, NIAID, NIH Virology Laboratory reported the isolation and characterization of one of the earliest broadly neutralizing antibodies (bnAbs), VRC01, from a single B cell of an HIV-infected, long-term, slow progressor donor [2]. Since then, applying similar strategies to serum banks from HIV-infected subject cohorts, multiple researchers have identified and characterized diverse bnAbs [13-20] and, in many cases, have extended their investigations to clinical trials.

Contemporaneous efforts and studies in anti-HIV mAb analysis, engineering, and functional and structural characterization have pinpointed previously unrecognized sites of vulnerability on the HIV envelope protein, informed efforts to develop broad and potent mAb therapeutics, and provided clarity and insight into requisite elements of an HIV-1 vaccine able to elicit potent and broad responses in recipients [15, 18, 21].

In parallel, the field of immunology has progressed in understanding of IgG subclasses, antibody domains, B cell ontogenies, and mAb-cell receptor interactions, including those with the neonatal Fc receptor (FcRn), which interacts with the fragment crystallizable (Fc) domain [22-24]. For biotherapeutic mAbs, strong pH-dependent FcRn binding capability is valued for its potentiation of longer mAb half-life and increased transcytosis across mucosal membranes.

Rational design methods coupled with high-throughput protein screening identified a variant of bevacizumab, a mAb that inhibits vascular endothelial growth factor, with a M428L/N434S (LS) substitution in the Fc domain that provided an 11-fold improvement in FcRn affinity at pH 6 and an extended serum half-life [25]. At the VRC, engineering this LS mutation into bnAb VRC01 produced VRC01LS, which demonstrated sustained levels in mucosal tissue relative to parental VRC01 in a simian-human immunodeficiency virus (SHIV) infection model [22] and in humans [26] (NCT02599896).

1.1. Next Generation HIV Envelope CD4 Binding Site Antibody Development: VRC01.23LS

At the VRC, advancing HIV mAb development efforts are typified by the generation and clinical evaluation of anti-HIV mAbs to the CD4 binding site (CD4bs) (VRC07-523LS, N6LS), the V2/V3 loop (CAP256V2LS), and the membrane proximal external region (10E8VLS) of the HIV-1 envelope protein.

More recently, to advance the HIV antibody field, the VRC has undertaken systematic engineering of the "next-generation" anti-HIV envelope antibodies, by combining a structure-based design and a matrix-based approach, with the aim to increase mAb breadth, potency, or both. Beginning with previously well-characterized and clinically studied bnAbs, panels of sequence variations are systematically generated and tested. Applying this approach to the CD4-binding site targeting bnAb VRC01LS, VRC01.23LS has been identified as a lead candidate for clinical evaluation. VRC01.23LS varies from parent VRC01LS by three sets of mutations:

- Heavy chain (HC,), G54W (glycine to tryptophan at HC residue 54), filling a hydrophobic pocket at the interface between VRC01LS and HIV-1 envelope (env) gp120,
- Extended HC Framework 3 (FR3) loop, adopted from VRC01 mAb class member VRC03, that increases contact surface area between the FR3 loop and a neighboring HIV-1 env gp120 protomer, and
- Deletion of the light chain (LC) N-terminal-most three amino acids to reduce potential steric clashes with the variable V5 region of HIV-1 env gp120.

On a 208 HIV- pseudovirus cross-clade panel, in comparison to VRC01LS, VRC01.23LS exhibits overall ~8-fold greater neutralization potency with a geometric mean IC_{50} of 0.042 μg/mL, and 94% breadth at IC_{50} of <1 μg/mL [27]. Serum concentrations of VRC01.23LS and VRC01LS in human FcRn knock-in mice were comparable [27]. Data from a study in cynomolgus macaques support the comparability of VRC01LS and VRC01.23LS PK. VRC01LS has a half-life (t1/2) of 71 ± 18 days in humans, and a comparable human t1/2 is expected for VRC01.23LS. Based on substantial PK data acquired from evaluating the LS mutation incorporated in multiple VRC mAbs, the LS modification has been retained in VRC01.23LS to increase pH-dependent FcRn binding and hence to increase antibody half-life *in vivo*.

1.2. Previous Human Experience

This study constitutes the first-in-human trial with VRC01.23LS; there is no previous experience with this mAb product in humans. Similar to its VRC mAb antecedents, VRC01.23LS targets

the CD4-binding site on the HIV-1 envelope protein, and, therefore, previous human experience with the first mAb in this class, VRC01, and its offspring, VRC01LS, provide relevant experience.

1.3. Parental VRC01, VRC01LS Safety in Clinical Trials

VRC01LS, a parental mAb of VRC01.23LS, differs from its antecedent, VRC01, by the two-amino acid mutations, LS, that increase binding to FcRn and extend mAb in vivo half-life. The two mAbs are otherwise identical in sequence.

1.3.1. VRC01

VRC01, the original VRC broadly neutralizing HIV-1 CD4bs mAb isolated from a subject, has been clinically evaluated in 15 trials, including Phase 1 studies VRC 601 (NCT01950325); VRC 602 (NCT01993706); and HVTN 104 (NCT02165267) and Phase 2 studies HVTN 704/HPTN 085(NCT02716675) and HVTN 703/HPTN 081 (NCT02568215).

As of March 2019, VRC01 has been administered either IV or SC at doses up to 40 mg/kg to over 3260 HIV-uninfected healthy adults, 110 HIV-1-infected adults, 39 HIV-1 exposed infants and 6 HIV-1 infected infants. There have been no serious adverse events (SAEs) related to VRC01, as assessed by the Sponsor.

1.3.2. VRC01LS

VRC HIV-1 human bnAb VRC01LS, the parent of VRC01.23LS, has been evaluated in five clinical trials. As of August 30, 2021, 112 subjects have received one or more doses of VRC01LS. VRC01LS IV and SC administrations have been well-tolerated in adults and children; there have been no SAEs related to VRC01LS. Clinical information regarding VRC01LS is available under DAIDS IND 125494 (VRC 606, HVTN 116), DAIDS IND 140909 (Dual bnAb protocol), DAIDS IND 130804 (VRC 607), and in Gaudinski et al [26].

In the three prevention studies (VRC 606, HVTN 116, and P1112), 56 healthy adults and 21 HIV-exposed infants have received VRC01LS in doses ranging from 5 to 40 mg/kg IV and 5 mg/kg SC in adults and up to 100 mg/dose SC in infants. VRC 606, a VRC01LS phase I dose escalation study, has been completed and results published [26] (NCT02599896). HVTN 116, a phase I study to evaluate VRC01LS and VRC01 safety, tolerability, PK, and anti-viral activity in healthy adults has also been completed (NCT02797171). A phase I study, IMPAACT P1112, evaluating the safety and PK of VRC01, VRC01LS, or another CD4bs mAb, VRC07-523LS, in HIV-1 exposed infants, has completed investigational product (IP) administration (NCT02256631).

In the two therapeutic studies in HIV-positive subjects (VRC 607 and Dual bnAb treatment in children), seven HIV-viremic adults and 28 HIV-suppressed children have received VRC01LS at doses ranging from 10 to 40 mg/kg IV. VRC 607/A5378, a phase I single dose study evaluating the safety and anti-viral effect of VRC01LS and VRC07-523LS in HIV-infected viremic adults, has been completed (NCT02840474). VRC01LS continues to be studied in HIV-infected, virally suppressed children in a Phase1/2 study (Dual bnAb), administering VRC01LS and mAb 10-1074 (NCT03707977).

Collectively, safety data from these studies indicate that VRC01LS is safe and well tolerated at doses ranging from 5 mg/kg to 40 mg/kg. The overall safety profile is consistent with expected events for monoclonal antibodies, most commonly mild to moderate reactogenicity that occurs shortly after product administration and is self-limited. There have been no unexpected safety trends identified and no SAEs related to VRC01LS.

1.4. Rationale for the Study Design

Animal and *in vitro* models of HIV infection have suggested bNAbs reactive to antigenically diversified Env proteins expressed by quasispecies of circulating virus may hold significant promise as immunoprophylactic and/or therapeutic agents to prevent the subversive effects of HIV on the immune system. Based on substantial PK data, acquired by evaluating the LS mutations in multiple, next-generation VRC mAbs and confirming the effect on mAb half-life, the LS modification has been retained in VRC01.23LS to increase pH-dependent FcRn binding and hence to increase antibody half-life in vivo. VRC01.23LS varies from parent VRC01LS by three sets of mutations as described in 1.1. VRC01.23LS aims to be a next-generation CD4bs antibody with increased potency and breadth relative to parental VRC01LS, while maintaining its extended half-life and safety. In clinical trials, multiple VRC01-class antibodies, including VRC01, VRC01LS, VRC07-523LS, and N6LS, have demonstrated favorable safety profiles [16, 20, 27-29].

This study is the first-in-human trial to evaluate the safety, tolerability, dose, and PK of VRC01.23LS administered intravenously or subcutaneously. The dosages selected for evaluation of VRC01.23LS are based on prior experience with other CD4-binding site mAbs, VRC01 and VRC01LS, which were shown in several clinical trials (VRC 601, VRC 602) to be safe and well-tolerated at 5-40 mg/kg dosages given intravenously and at a 5 mg/kg dosage given subcutaneously in both HIV-infected and -uninfected adult populations [28, 29] . This study will involve the evaluation of VRC01.23LS administered alone or by repeat dosing.

While Groups 1 through 4 will receive a single dose of VRC01.23LS by SC injection or IV infusion, Groups 5 and 6 will receive three-repeat doses of VRC01.23LS at 12-week intervals (i.e., on Weeks 0, 12, and 24). A 12-week interval for repeat-dosing is based on predicted half-life and has been used in clinical trials with VRC01LS and VRC07-523LS [30]. Aligning the antibody dose levels and administration interval with that used in prior studies of other HIV-1 bNAbs will allow for a direct comparison of the serum concentration of each bNAb at identical time-points. This in turn will support PK profile comparisons and characterization of the bNAbs currently in development by the VRC. The PK of VRC01.23LS administered using different regimens, dosages, and routes will be evaluated in healthy adults aged 18 to 60 years.

1.5. Research-Specific Laboratory Assessments

The research assays described in this section are designed to characterize the investigational product rather than assess the health of the subjects. Laboratory assessments in this Phase 1 study will include PK analysis, evaluation for anti-drug antibody (ADA) development following product exposure, and ex vivo analysis to assess the neutralization activity of VRC01.23LS post-injection/infusion. Other assays may also be completed from 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. Some immunogenicity assays may be performed by VRC laboratories in Bethesda, MD, or by approved contract laboratories or research collaborators. See Appendix I for schedules, volumes and tube types to be used for research sample collection. Tube types for clinical laboratory evaluations and research collections are selected according to institutional requirements and are shown in the Schedule of Evaluations to estimate blood volumes. Different tube types and sizes may be used to meet site requirements. Samples will be transported according to approved site procedures.

1.5.1. Pharmacokinetic (PK) Analysis

The VRC01.23LS concentration for the PK analysis will be measured by a Meso Scale Discovery (MSD) or similar assay [22].

1.5.2. Anti-drug Antibody (ADA) Analysis

A three-level algorithm will be used to screen, confirm, and functionally characterize ADA to VRC01.23LS in clinical serum and/or plasma samples. Analysis will be conducted according to the Food and Drug Administration (FDA) guidance [31]. Screening and confirmation will involve a MSD electrochemiluminescence (ECL) bridging or similar assay [22]. The ADA assay will be conducted on batched samples collected at baseline, 4-weeks and 8-weeks in the single administration groups, with additional 28- and 32-weeks samples in multiple administration groups and may be tested at the last study visit if needed. It may also be assessed at other time-points if there is a clinical indication, or the PK analysis shows a substantial decrease in the VRC01.23LS concentration.

1.5.3. HIV Pseudovirus Neutralization

For all study groups, subject sera will be evaluated to assess the functional capacity of passively administered VRC01.23LS to neutralize pseudotyped HIV viruses using an *in vitro* cell-based virus neutralization assay, such as previously described for VRC01, VRC01LS, and VRC07-523LS [28-30, 32, 33].

1.5.4. Allotype-Specific Effects

Exploratory evaluation to detect theoretical immunoglobulin G1 (IgG1) allotype-specific effects may be performed in cases when PK measures suggest a reduced VRC01.23LS antibody half-life or an ADA response [34-36]. Coded stored samples will be used for evaluation of the genetic sequence of the immunoglobulin heavy chain constant region allotype.

2. INVESTIGATIONAL PRODUCTS

This protocol will evaluate the investigational product, VRC-HIVMAB0115-00-AB (VRC01.23LS), in healthy adults.

2.1. VRC01.23LS (VRC-HIVMAB0115-00-AB)

2.1.1. Overview

VRC-HIVMAB0115-00-AB (VRC01.23LS) is manufactured under current Good Manufacturing Practices (cGMP) by VRC/NIAID/NIH at the VRC Pilot Plant operated under contract by the Vaccine Clinical Materials Program, Leidos Biomedical Research, Inc., Frederick, MD.

VRC01.23LS is a recombinant human immunoglobulin G1 (IgG1) antibody, targeting the HIV envelope CD4 binding site.

2.2. NONCLINICAL STUDIES

A summary of non-clinical studies conducted with VRC01.23LS is presented in the table below. More information related to non-clinical evaluations of VRC01.23LS can be found in the IB.

Table 1: Non-Clinical Studies Summary

Study Purpose	Study Outcome
In Vitro Neutralization Activity	On a 208 HIV-pseudovirus cross-clade panel, in comparison to VRC01, VRC01.23LS exhibits an overall ~8-fold greater neutralization potency with a geometric mean IC_{50} of 0.042 µg/mL, and 94% breadth at IC_{50} of <1 µg/mL.
VRC01.23LS Serum Levels in Mice	In human FcRn transgenic mice, VRC01.23LS exhibited a serum half-life ($t_{1/2}$) comparable to that of parental VRC01LS.
Non-human primate (NHP) PK	Three cynomolgus monkeys received a single IV dose of 10 mg/kg VRC01.23LS. Two of the monkeys exhibited PK comparable to that of parental VRC01LS. One monkey exhibited depletion beginning on day 20, suggesting induction of an ADA response. No signs of toxicity were observed.
Tissue Cross Reactivity (TCR) Study	In a GLP TCR study evaluating a panel of 38 normal human tissues obtained from at least 3 adult donors per tissue, VRC01.23LS did not exhibit specific cell membrane binding in any human tissue, which was expected and was consistent with similar lack of binding observed for VRC01 and VRC01LS.
Autoreactivity by assessment of binding to a human epithelial cell line (HEp-2) by indirect immunohistochemistry	VRC01.23LS demonstrated no evidence of autoreactivity as assessed by HEp-2 cell binding.
Autoreactivity by assessment of anti-phospholipid reactivity	VRC01.23LS was considered not reactive in the cardiolipin binding assay when compared to an anti-HIV neutralizing mAb (4E10), known to react with phospholipids.

3. STUDY OBJECTIVES

3.1. Primary Objectives

- To evaluate the safety and tolerability of VRC01.23LS in healthy adults when administered SC as a single dose at 5 mg/kg.
- To evaluate the safety and tolerability of VRC01.23LS in healthy adults when administered IV as a single dose at 5, 20, or 40 mg/kg.
- To evaluate the safety and tolerability of VRC01.23LS in healthy adults when administered by repeat SC dosing at 5 mg/kg, for a total of 3 injections in 12-week intervals.
- To evaluate the safety and tolerability of VRC01.23LS in healthy adults when administered by repeat IV dosing at 20 mg/kg, for a total of 3 infusions in 12-week intervals.

3.2. Secondary Objectives

- To evaluate the pharmacokinetics of VRC01.23LS at each dose level and route of administration throughout the study.

3.3. Exploratory Objectives

- To determine whether anti-drug antibody (ADA) to VRC01.23LS is detectable in recipients at specific timepoints throughout the study.
- To assess the neutralization potential of VRC01.23LS at timepoints throughout the study.
- To assess for IgG1 allotypes and allotype-specific effects on PK as appropriate.

4. STUDY DESIGN AND CLINICAL PROCEDURES

This is an open-label, dose-escalation study to examine the safety, tolerability, dose, and PK of VRC01.23LS in healthy adults as shown in the study schema (Table 2).

Table 2: VRC 615 Study Schema

VRC 615 Study Schema					
Group	**Subjects**	**VRC01.23LS Dose and Route**	**Dosing Schedule**		
			Day 0	**Week 12**	**Week 24**
1	3	5 mg/kg IV	X		
2	3	5 mg/kg SC	X		
3	3	20 mg/kg IV	X		
4	3	40 mg/kg IV	X		
5	5	5 mg/kg SC	X	X	X
6	5	20 mg/kg IV	X	X	X
Total	22*	*Enrollment up to a total of 40 subjects is permitted if additional subjects are necessary for safety or PK evaluations.			

The study will be conducted at a single site, the Vaccine Evaluation Clinic located at the NIH Clinical Center (NIH CC).

Enrollment will begin with the 5 mg/kg dose groups (Groups 1, 2 and 5) with no more than one subject per day at the 5 mg/kg dose for the first 3 subjects. Enrollments into the subsequent dose groups (Groups 3, 4, and 6) will proceed after dose-escalation reviews as described in 4.4.

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. All inclusion and exclusion criteria must be met for eligibility.

4.1.1. Inclusion Criteria

***A subject must meet all of the following criteria**:*

1. Willing and able 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 60 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. Adequate venous access if assigned to an IV group or adequate abdominal subcutaneous tissue if assigned to SC group.
8. Willing to have blood samples collected, stored indefinitely, and used for research purposes.

Laboratory Criteria within 56 days prior to enrollment:

9. White blood cell count (WBC): 2,500-12,000/mm3.
10. WBC differential either within institutional normal range or accompanied by the Principal Investigator (PI) or designee approval.
11. Platelets: 125,000 – 500,000/mm3.
12. Hemoglobin within institutional normal range or accompanied by PI or designee approval.
13. Creatinine: ≤ 1.1 x Upper Limit of Normal (ULN).
14. ALT: ≤ 1.25 x ULN.
15. AST: ≤ 1.25 x ULN.
16. Negative for HIV infection by an FDA approved method of detection.

Female-Specific Criteria:

17. Agrees to use an effective means of birth control from 21 days prior to enrollment through the duration of study participation.
18. Negative β-HCG (human chorionic gonadotropin) pregnancy test (urine or serum) on day of enrollment for women presumed to be of reproductive potential.

4.1.2. Exclusion Criteria

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

1. Woman who is breast-feeding or planning to become pregnant during study participation.
2. Weight > 115 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. Receipt of any investigational study product within 28 days prior to enrollment (Note: Emergency Use Authorization of a COVID-19 vaccine is not exclusionary).
6. Receipt of an investigational HIV vaccine or anti-HIV monoclonal antibody.
7. Receipt of any live attenuated vaccine within 28 days prior to enrollment.
8. Receipt of any vaccine within 2 weeks prior to enrollment.

9. 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.
10. 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, infectious disease, autoimmune disease, psychiatric disorder, heart disease, or cancer.

4.2. Inclusion of Vulnerable Subjects

4.2.1. Pregnant Women

This is a first-in-human trial in healthy subjects, ≥18 years of age. Because the effects of the vaccine on the fetus are not known, pregnant women will not be eligible for the trial. Women of childbearing potential must utilize a highly effective method of contraception and will be required to have a negative urine or serum pregnancy test within 24 hours prior to each product administration.

Pregnancy, if it occurs during study participation, will be recorded in the study database. These participants will not continue to receive any further study product administrations, **Error! Reference source not found.** research sample collections, or research procedures. Pregnant participants will continue to be followed for clinical safety and to collect the pregnancy outcome. Any follow-up procedures and/or data collected will be for clinical/safety outcome purposes only. Pregnancy will be reported as described in Section 5.6.

4.2.2. Participation of Children

Children are not eligible to participate in this clinical trial because the study agent 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.

4.2.3. Participation of 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 an NIH staff member seeks to enroll in research taking place within their own work unit or conducted by any of their supervisors, the employee will be:

- Informed that neither participation nor refusal to participate as a research subject will have an effect, either beneficial or adverse, on the subject's employment, training or position at the NIH,

- When possible, consent should be obtained by an individual in a non-supervisory relationship with the subject, and
- When consent is conducted, a third party (e.g. a consent monitor) will be included through the Bioethics Consultation Service or another party independent of the research team or, if a consent monitor is not available, the consent process will be observed by another qualified investigator on the study who is independent of the NIH staff member's work unit and not a supervisor to the NIH staff member. If no such person exists, consent observation may be performed by any qualified investigator on the study. Protocol study staff will be trained on obtaining potentially sensitive and private information from co-workers or subordinates.

4.2.4. Adult Subjects who Lack the Capacity to Consent

Adults who are unable to provide initial informed consent are not eligible 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 4.5

4.3. Clinical Procedures

Evaluation of study product safety will include laboratory studies, medical history, and physical assessment by clinicians, and subject self-assessment on a diary card for 7 days after product administration. The study schedule is provided in the Schedule of Evaluations, Appendix I. Total blood volume drawn from each subject will comply with the NIH CC Guidelines, which is available on the NIH intranet at the following link: http://cc-internal.cc.nih.gov/policies/PDF/M95-9.pdf. 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.

The study will be conducted at the Vaccine Evaluation Clinic (VEC) located at the NIH CC. All nursing staff in the VEC are assessed annually for nursing competency including medication administration, peripheral vascular access device care and maintenance, and clinical emergency response. The VEC Clinic is equipped with basic cardiac life support equipment and emergency medications. An advanced clinician (nurse practitioner, physician assistant or physician) is available in the clinic during administration of all investigational study products and throughout the post-administration monitoring period.

4.3.1. Recruitment and Retention Strategies

Study enrollments will be conducted at the NIH Clinical Center. Study subjects will be recruited through the VRC's screening protocol, VRC 500 (NCT 01375530). The on-site and off-site Institutional Review Board (IRB)-approved advertising will be implemented.

Per recruitment plan described in the VRC 500 protocol, efforts will be made to include women and minorities in proportions similar to that of the community from which they are recruited. The recruitment team utilizes a variety of mechanisms to recruit participants including flyer distribution within and outside of the NIH, social media, community tabling events, print and radio ads, listserv emails, posting information on the NIAID/ VRC website, and ResearchMatch.org to effectively recruit potential volunteers.

4.3.1.1. Costs

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

4.3.1.2. Compensation

Subjects will be compensated for time and inconvenience in accordance with the standards for compensation of the NIH CC Clinical Research Volunteer Program. Compensation for a study visit that includes IV product administration is $430; a study visit that includes SC 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 all 7 days of the electronic diary card. The total amount of compensation varies depending upon the group and the visits completed.

4.3.2. Screening

All screening procedures for this study are described and will be completed through the Vaccine Research Center's screening protocol, VRC 500 (NIH 11-I-0164) used for all VRC IND studies conducted at the NIH Clinical Center. The Recruitment Plan per NIH Policy 302 for all VRC studies can be found in the NIH IRB approved VRC 500 protocol. Subjects will be recruited through Institutional Review Board (IRB)-approved advertising. Screening evaluations performed to determine eligibility for study participation will include medical history review, physical exam, and the clinical laboratory tests as detailed in the Schedule of Evaluations, Appendix I). No screening procedures will be done under protocol VRC 615.

Additional assessments of health may be conducted at screening based on clinical judgment. Screening evaluations for specific eligibility criteria must be completed within the time interval specified prior to enrollment for the given parameter and may be repeated, as needed, to confirm eligibility.

Blood samples for research can be drawn at any time during the screening period and are not subject to a time interval. Informed consent documents will be reviewed. Counseling related to potential risks of the study product, pregnancy prevention, and HIV risk-reduction will be performed. An Assessment of Understanding (AoU) will be completed in association with enrollment into VRC 615. Screening records will be maintained to document the reason why an individual was screened but not enrolled.

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 as described in Sections 4.3.4 and 4.3.9.

4.3.3. Enrollment, Study Days and Visit Numbers

In this study, enrollment is defined as the assignment of a study identification number and study group schedule in the clinical database. A clinician will discuss the target dates and timing of the study product administration(s) 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.

Day 0 is defined as the day of first VRC01.23LS administration. Day 0 may occur on the same day as enrollment or up to 6 weeks after enrollment. This period may be increased with PI approval. 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 to Day -42). 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 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.

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

4.3.4. Administration of VRC01.23LS

All study product administrations will be completed according to the assigned group. Licensed vaccines should be avoided within 2 weeks before and after product administration. Prior to administering study product, a clinician should consult with an advanced practitioner if licensed vaccination occurred or is scheduled within that time frame.

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

4.3.4.1. IV Administration

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. VRC01.23LS will be administered with approximately 100 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. At the end of product administration, the IV administration set must be flushed with about 30 mL (or appropriate volume) of normal saline under the same infusion rate to ensure the entire dose is given.

4.3.4.2. SC Administration

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 5.75 mL. The SC dose will be administered by standard needle in a maximum volume of about 2.5 mL per injection site. Up to three (3) SC injection sites may be used if deemed necessary by the clinician. SC administration sites should be at least 2 inches apart.

4.3.5. Post-Product Administration Follow-up

Following completion of IV product administration in Groups 1, 3, 4, and 6, subjects will be observed for at least 2 hours in the clinic. Following completion of SC product administration in Groups 2 and 5, subjects will be observed for at least 1 hour in the clinic.

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 and Clinical Follow-up

Each subject will be given a 7-day diary (paper and electronic-based available), a thermometer, and a measuring tool. The subjects will use the diary to record their highest temperature, local and systemic symptoms, and concomitant medications taken for 7 days after any 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 reactogenicity. Completion of diary card training will be noted in the source documents. The web-based diary for this study is entered in the electronic database provided by Emmes Corporation via a NIAID approved contractual agreement. No personal identifiable information (PII) is entered in this database. The secure web-based electronic method is preferred for diary completion, but 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 diary will include systemic events of temperature, feeling unusually tired/unwell, muscles aches (outside the injection site), headache, chills, nausea and joint pain; and local event at the product administration site of pain/tenderness, swelling, redness, bruising, and pruritus. Subjects will record their highest measured temperature daily for assessment of fever and largest measured diameter of redness, swelling, and bruising at the injection site, if applicable. Subject diaries will be reviewed by a clinician for accuracy and completeness at follow-up visits. Clinicians will follow and collect resolution information for any reactogenicity symptoms that are not resolved within 7 days.

Diary card data will be available in real-time 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 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 (ADL) (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.

Clinical laboratory assays and clinical evaluations will assess safety and tolerability at specified intervals after each administration. Throughout the study, clinicians will also assess subjects for any changes in symptoms. Any new or concerning symptoms will be fully assessed to include specialty consultation at the NIH Clinical Center as indicated clinically.

4.3.7. Pharmacokinetics

PK samples will be collected as close as reasonably possible to the target timepoints. However, actual time of collection is critical for PK analysis and will be recorded for all samples. The PK timepoints are shown in the Schedule of Evaluations (Appendix I).

4.3.8. Follow-Up through End of Study

The Schedule of Evaluations (Appendix I) provides details on the study schedule and the allowable windows for completing study visits. Study follow-up will continue via clinical visits through 24 weeks after the final product administration. The visit schedule is based on intervals of time after product administration. 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.

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.

If product administration is discontinued for a Group 5 or 6 subject assigned to receive repeat product administrations, then the study schedule may be modified, and the subject will be followed for 24 weeks after the last product administration received. Schedule 5 of the SOE outlines this altered schedule. Briefly, subjects will be followed according to the assigned group visit schedule until the 12th week after their last product administration and will then complete the protocol according to Schedule 5 starting at Visit 11 for those who receive only one product administration or Visit 17 for those who receive two product administrations.

Additional visits and blood draws may be scheduled during the study if needed to assess subject safety or for sample collection for immunological testing. Any evaluation for an AE or possible exacerbation of a pre-existing condition may be evaluated at study team discretion as a "protocol related" evaluation.

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.

4.3.9. 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. Receipt of an FDA-approved vaccine at any time during the study will be recorded in the database. Clinicians should work with subjects regarding the timing of licensed vaccines relative to study product administration as indicated in4.3.4. Otherwise, concomitant medication changes throughout the study will be recorded in the subject's chart as needed for general medical documentation but will not be recorded in the database.

4.4. Criteria for Dose-Escalation

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.

Table 3: Plan for Dose-Escalation Reviews

Data Review Objective	Minimum Evaluable Safety Data*	Favorable Review Outcome
Review #1		
• Dose-escalation from 5 to 20 mg/kg IV	• All post-administration safety data from Day 0 through at least the "Day 7" visit in at least 3 5-mg/kg IV recipients from Group 1.	• Proceed with enrollment into Groups 3 and 6.
Review #2		
• Dose-escalation from 20 to 40 mg/kg IV	• All post-administration safety data from Day 0 through at least the "Day 7" visit in at least 3 20 mg/kg IV recipients from Groups 3 or 6.	• Proceed with enrollment into Group 4.

Group 2 and Group 5 enrollment (5 mg/kg SC) does not depend on 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, then additional subjects may be enrolled to have the requisite data on at least 3 subjects at the dose level and route being evaluated. Additionally, AEs assessed as related to the study product at the time of a dose-escalation review may be judged by the PSRT to warrant adding additional subjects to a particular group. Consultation with the IRB or FDA as per study pause criteria may occur if indicated.

4.5. Criteria for Subject Discontinuation from Protocol Participation

Subjects who receive at least one dose of VRC01.23LS will be encouraged to stay on the study and complete safety evaluations. A subject may be discontinued from protocol participation for the following reasons:

- Subject voluntarily withdraws;
- Pregnancy;
- The IND Sponsor or regulatory authorities stop the study;
- The PI assesses that it is not in the best interest of the subject to continue participation in the study; or
- Severe non-compliance as determined by the PI.

4.6. Criteria for Discontinuation of VRC01.23LS Administration

Under certain circumstances, a subject may be prohibited from receiving further study product administrations. These include:

- Grade 3 adverse event assessed as related to VRC01.23LS (with the exception of self-limited Grade 3 solicited reactogenicity that resolve during the solicited reactogenicity period);
- Grade 4 adverse event assessed as related to VRC01.23LS;
- SAE assessed as related to VRC01.23LS;
- Immediate hypersensitivity reaction associated with VRC01.23LS;
- Intercurrent illness that is not expected to resolve prior to the next scheduled study product administration and for which PI (or designee) believes is in the best interest of the subject to restrict further exposure;
- Repeated failure to comply with protocol requirements.

Subjects who receive at least one dose of VRC01.23LS but are discontinued from further study product administrations will continue with follow-up as shown in the Schedule 5 of the Schedule of Evaluations with the exception that research sample collections will be discontinued for pregnant women or others in which it is contraindicated.

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 and severity of adverse events (AEs). Study product administrations and new enrollments will be paused if any of the following criteria are met:

- **One** (or more) subject experiences a serious adverse event (**SAE)** that is assessed as related (possible, 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 (possible, probably, or definitely) to study agent (other than self-limited Grade 3 AEs that resolve during the solicited reactogenicity period).

In the event of a pause, the IND Sponsor Medical Officer (MO) and the PSRT will be promptly notified.

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 Medical Officer (MO), with participation by the PI, will conduct the review and make the decision to resume, amend or close the study. The IRB and FDA will be notified 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 EVENTS

5.1. Adverse Events

An adverse event (AE) is 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 4.3.6) will be recorded without attribution assessments by the subject on paper or electronic diary for 7 days after each product administration.
- Unsolicited AEs will be recorded in the study database with attribution assessments from product administration through the Day 28 post-product administration visit.
- SAEs (as detailed in 5.2) and new chronic medical conditions will be recorded as AEs through the last expected study visit or contact.

Appendix II describes how the relationship between an AE and the study product will be assessed. Also available in Appendix II is the link to the 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 adverse event or life-threatening suspected adverse reaction. An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death. "Life-threatening" refers to an AE that at occurrence represents an immediate risk of death to a subject. It does not include an adverse event 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
- 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 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 adverse event for which there is a reasonable possibility that the drug caused the adverse event.
- *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; 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 312.32.

5.5. Reporting to the Institutional Review Board

The following information is consistent with NIH IRB Policy 801: Reporting Research Events.

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, and
- New information that might affect the willingness of subjects to enroll or continue participation in the study.

5.5.1. Unanticipated Problem (UP) Definition

An unanticipated problem (UP) is defined as any incident, experience, or outcome that meets **all** of 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 Definition

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 affects 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 Definition

A protocol deviation is defined as any change, divergence, or departure from the IRB-approved research protocol and is 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.

5.6. Reporting of Pregnancy

Pregnancy is not an adverse event, but pregnancy, if it occurs during the time of study participation, will be recorded in the study database, and notification on the pregnancy will be distributed to the study team and to the IND Sponsor. Subjects will be followed for clinical safety and to collect the pregnancy outcome as described in Section 4.2.1. Congenital abnormalities or birth defects and spontaneous miscarriages that meet serious criteria (Section **Error! Reference source not found.**) will be reported as SAEs. Pregnancy outcome will be reported to the IND Sponsor and to regulatory agencies.

6. STATISTICAL CONSIDERATIONS

6.1. Overview

This is a phase I, open-label, dose-escalation study in healthy adults to assess the safety, tolerability, dose, and PK of VRC01.23LS (VRC-HIVMAB0115-00-AB), a human monoclonal antibody with broad HIV-1 neutralizing activity.

6.2. Accrual and Sample Size Considerations

Recruitment will target about 22 healthy adults, 18 to 60 years of age, with 3 subjects in each of the single dose groups (Groups 1 through 4) and 5 subjects in the repeat dose groups (Groups 5 and 6) as shown in **Table 2**. The permitted accrual is 40 subjects in total to allow for additional enrollments in the event that an enrolled subject does not complete the minimum evaluations needed to meet the protocol criteria for the group dose safety or dose-escalation evaluation. Dose escalation rules are described in 4.4.

6.2.1. Group Assignments

The Advantage eClinical system (The Emmes Company LLC, Rockville, MD) will be used to assign subjects to a dose group in active accrual at the time of enrollment. If an enrolled subject discontinues from the study before he/she has received study product, a new eligible subject may be enrolled into the same group. If a replacement subject is needed in the case of a subject withdrawal, the replacement subject will be assigned to the same group as the dropout subject.

6.2.2. Sample Size Considerations

The goal of the safety evaluation is to identify safety concerns associated with product administration. The ability of the study to detect SAEs can be expressed by the true event rate above which at least 1 SAE would likely be observed and the true event rate below which no events would likely be observed. For this study, group sizes are targeted to be n=3 or n=5, and within this section, an event is defined as a subject experiencing at least one event.

For n=3, there is at least a 90% chance of observing at least 1 event if the true rate is 0.536 or more and at least a 90% chance of observing no events if the true rate is 0.035 or less. For n=5, there is at least a 90% chance of observing at least 1 event if the true rate is 0.369 or more and at least a 90% chance of observing no events if the true rate is 0.021 or less.

Probabilities of observing 0, 1 or more, and 2 or more events among group sizes n=3 and n=5 are presented in **Table 4** for a range of possible true event rates. These calculations provide a more complete picture of the sensitivity of this study design to identify potential safety problems with product administration.

Table 4: Probability of Observing a Given Number of Events for Different True Event Rates

True event rate	N=3			N=5		
	Pr (0 events)	Pr (1+ events)	Pr (2+ events)	Pr (0 events)	Pr (1+ events)	Pr (2+ events)
0.01	0.970	0.030	<0.001	0.951	0.049	0.001
0.05	0.857	0.143	0.007	0.774	0.226	0.023
0.10	0.729	0.271	0.028	0.590	0.410	0.081
0.20	0.512	0.488	0.104	0.328	0.672	0.263
0.30	0.343	0.657	0.216	0.168	0.832	0.472
0.40	0.216	0.784	0.352	0.078	0.922	0.663

Table 5 displays the two-sided 95% confidence intervals (CIs) for the probability of an event based on observed events for n=3 and n=5 using the exact method. For example, if none of the subjects experience a particular safety event, the 95% two-sided upper confidence bound for the true rate of such events in the population is 0.708 for n=3 and 0.522 for n=5.

Table 5: Two-sided 95% Confidence Intervals for Probability of an Event Based on Observed Event Rate

Observed event rate	95% CI for N=3	Observed event rate	95% CI for N=5
0/3	0.000, 0.708	0/5	0.000, 0.522
1/3	0.008, 0.906	1/5	0.005, 0.716
2/3	0.094, 0.992	2/5	0.053, 0.853
3/3	0.292, 1.000	3/5	0.147, 0.947
-	-	4/5	0.284, 0.995
-	-	5/5	0.478, 1.000

6.3. Statistical Analysis

6.3.1. Analysis Variables

The analysis variables will consist of baseline, pharmacokinetics, and safety variables to support analyses of the primary and secondary objectives. Continuous variables will be summarized using descriptive statistics, and categorical variables will be summarized using counts and percentages.

6.3.2. Baseline Characteristics

Descriptive statistics will be used to summarize baseline characteristics, inclusive of demographics and safety laboratory measurements.

6.3.3. Safety Analysis

Subjects who receive at least one administration will be considered in the safety analyses.

Solicited Adverse Events: Solicited AE data will be collected for 7 days after each product administration. When summarizing the number and percentage of subjects experiencing each

solicited sign or symptom, subjects with multiple occurrences of the same event will be counted once, and only the maximum severity level will be presented. Solicited AEs will be summarized by route and dose level for each administration.

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 percentage of subjects with each unsolicited AE will be summarized by group (Groups 1 through 6). Subjects with multiple occurrences of the same event will be counted once; only the maximum severity level will be presented in severity summaries, and the strongest relationship level will be presented in relationship summaries.

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, onset study day, duration, and outcome.

Local laboratory values: By-subject listings will present laboratory data measured during the course of the study and may include change from baseline values and reference ranges for abnormal findings.

Additional listings may be included, such as disposition and administration status, concomitant medications, protocol deviations, or vital signs.

6.3.4. Tolerability Evaluation

The tolerability of an investigational medicinal product represents the degree to which overt adverse effects can be tolerated by the subject [32]. Since VRC 615 is the first trial of VRC01.23LS in healthy adults, the tolerability evaluation will include mostly descriptive summaries of the frequency of solicited AE reports with an onset in the 3 days following each administration and subject withdrawals or discontinuations based upon subject discomfort or AEs. This early assessment of tolerability will inform the parameters to solicit or routinely assess in future studies to further characterize the tolerability profile in a larger subject cohort.

6.3.5. Pharmacokinetics Analysis

Blood samples for PK evaluations will be collected at time points based on participant study groups defined in the Schedule of Evaluations (Appendix I).

Individual Subject Pharmacokinetic Analysis**:**

Population pharmacokinetic analyses will be performed on the VRC01.23LS pharmacokinetic data following product administration to determine compartmental PK parameters as previously described [37-39]. One, two and three compartment pharmacokinetic models will be considered. Based on prior pharmacokinetic studies of bnAbs, including VRC01LS, 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). Given the small subject numbers, the population PK analysis will include only a limited covariate analysis to assess clinical factors as fixed effects associated with VRC01.23LS PK parameters. Specifically dose level, repeat dosing and allotype will be assessed as applicable. 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 and Monte Carlo simulations will be utilized to assess dosing strategies to archive target VRC01.23LS concentrations.

Population Pharmacokinetic Analyses**:**

Population pharmacokinetic analyses will be performed on the VRC01.23LS pharmacokinetic data following product administration to determine compartmental PK parameters as previously described [26, 37, 40]. One, two and three compartment pharmacokinetic models will be considered. Based on prior pharmacokinetic studies of bNAbs, including VRC01LS, 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 (Vd1 and Vd2), inter-compartmental clearance (Q), CL and bioavailability (F). Given the small subject numbers, the population PK analysis will include only a limited covariate analysis to assess clinical factors as fixed effects associated with VRC01.23LS PK parameters. Specifically dose level, repeat dosing and allotype will be assessed as applicable. 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 and Monte Carlo simulations will be utilized to assess dosing strategies to archive target VRC01.23LS concentrations

6.3.6. Interim Analyses

Preliminary PK analyses may be done as the data for each dose level is obtained. This may be performed before a dose group's PK data is complete and may only generate a subset of the final PK parameters. The interim analyses may be used to inform decisions about the dose levels to be administered in future studies.

6.3.7. Missing Data

Missing data will be assumed to be missing completely at random. Analyses will include all samples available at each study time point. Based on experience from previous trials, we expect missing data to be rare. Regardless, in the event of missing data, we will report the occurrence and extent of missingness. We will also provide plausible explanations for the missingness mechanism, should such information be available.

7. PHARMACY PROCEDURES

The dose groups and VRC01.23LS dosing schedule are shown in **Table 1**.

7.1. Study Product

VRC01.23LS (VRC-HIVMAB0115-00-AB) is a clear, colorless to yellow liquid, sterile aqueous buffered solution that is essentially free of visible particles (some opaque or translucent particles may be present) and is filled into 10 mL single-dose vials. Each vial contains a 6.25 ± 0.1 mL volume of VRC01.23LS at a concentration of 100 ± 10 mg/mL in formulation buffer composed of 20 mM Acetate Phosphate, 25 mM NaCl, 150 mM Arginine HCl, 5% Sucrose, 0.2% Polysorbate 80, pH 5.8.

7.2. VRC01.23LS Vialed Product Storage

VRC-HIVMAB0115-00-AB (VRC01.23LS) vials are stored until use at -35°C to -15°C in a qualified, continuously monitored, temperature-controlled freezer. Following thaw, unopened VRC01.23LS vials may be stored for up to 24 hours at ambient temperature (up to 27°C) and up to 14 days at 2°C to 8°C. Product may not be stored in direct sunlight. If stored at 2°C to 8°C, vials must be equilibrated to 15°C to 27°C for a minimum of 60 minutes and may be held at this temperature for up to 8 hours prior to product preparation. Vials should not the refrozen after thaw.

7.3. Temperature Excursions

The site pharmacist must promptly report any storage temperature excursions outside of the normal allowance for the investigational products to the IND Sponsor. In the case of storage or shipping/handling temperature excursions outside of the normal allowance for the storage device, the following procedure is to be followed:

1. Quarantine the affected product in a separate area. If the excursion results in thawed material, it must not be refrozen. Thawed vials must be quarantined at 5°C ± 3°C.
2. Report the excursion to the IND sponsor's authorized representative (SAR) or designee, any other parties required by site procedures, and via email to VRCProductinquiries@nih.gov. Quarantine the product and do not use until the IND Sponsor's authorized representative or designee informs the site pharmacist whether continued clinical use of the product is acceptable.
3. Inquiries sent to VRCProductinquiries@nih.gov will prompt an automatic email reply to the notifier that includes the Clinical Excursion Reporting Form (CERF) as an attachment.
4. Fill out the CERF as completely as possible, either electronically or manually.
5. Email the completed form and relevant attachments (e.g., temperature charts) to VRCProductinquiries@nih.gov, replying to the previous email.
6. After receipt and evaluation of the reported information, the Sponsor or manufacturer's designee will notify the site pharmacist whether continued clinical use of the product is acceptable.

7.4. Preparation of VRC01.23LS for Administration

This section describes how the site pharmacist will prepare the study products for administration and how the clinician will administer each product. Clinician instructions on how to select an administration site are in Sections 4.3.4.1 and 4.3.4.2

7.4.1. Thawing Instructions

Prior to each dose preparation, the pharmacist will calculate the dose per Study Schema and retrieve the minimum number of vials required to prepare each dose. Thaw and equilibrate the vials at 15°C to 27°C for a minimum of 60 minutes. If thawed vials are removed from refrigerator at 2°C to 8°C, equilibrate at 15°C to 27°C for a minimum of 30 minutes and may be held at this temperature for up to 8 hours prior to product preparation. Vials should be gently swirled for approximately 30 seconds while avoiding foaming. Vials should not be shaken.

7.4.2. Preparation for Intravenous Infusion

To prepare the IV infusion, the calculated dosing volume must be mixed with 100 mL 0.9% Sodium Chloride Injection USP (equivalent to DEHP-free and Latex-free B.Braun PAB® REF# S8004-5264). It is acceptable that the prefilled infusion bag may have varying amount of overfill depending on the manufacturer, pharmacy may follow the institutional practice to account for the overfill to ensure the final concentration is maintained between the range of 2.15 mg/mL to 31.5 mg/mL. Purge all air from the IV bag before adding VRC01.23LS into the bag. A primary infusion set attached with in-line filter must be used for IV product administrations and comply with the following specifications: DEHP-free, Latex-free primary infusion set (equivalent to BD Alaris Pump Infusion Set REF# 2426-0007), 1.2-micron polyethersulfone (PES) filter membrane (equivalent to B.Braun REF# 473994 filter extension set). The entire administration set must then be primed by the final solution.

The prepared IV bags may be stored for up to 4 hours at 2ºC to 8ºC or at ambient temperature (up to 27°C), including dose administration time.

7.4.3. Preparation for Subcutaneous Injection

To prepare the subcutaneous injection, the calculated dosing volume must be withdrawn from the thawed vial(s) into 1 to 3 syringes using 5-micron filter needle(s). A new filter needle must be used for measuring the required volume up to 2.5 ml for each syringe. The filter needle must be discarded prior to dispensing and replaced with a needle suitable for subcutaneous injection at the time of dose administration. The prepared syringe may be stored at 2ºC to 8ºC or at ambient temperature (up to 27°C) for up to 4 hours, including dose administration time.

7.5. Labeling of Study Product

Vials of both study products 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.

7.6. Study Product Accountability

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

7.7. Study Product Disposition

Empty vials, including equipment used to prepare VRC01.23LS, and the unused portion of a vial will be discarded in a biohazard containment bag for incineration or decontamination by autoclave and disposed in accordance with the institutional or pharmacy policy. Partially used vials will not be administered to other subjects or used for *in vitro* experimental studies. Any unopened vials that remain at the end of the study will be returned or discarded at the discretion of the sponsor in accordance with policies that apply to investigational agents.

8. HUMAN SUBJECT PROTECTIONS AND ETHICAL OBLIGATIONS

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

8.1. Informed Consent

The study informed consent (ICF) is provided as a separate hard copy which 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 before any protocol- specific procedures or study product is administered. The Assessment of Understanding (AoU) must be completed before the study ICF is signed.

The study informed consent form (ICF) describes the investigational product to be used and all aspects involved in protocol participation. It is provided to potential participants for their review in advance, typically as a hard copy during screening as described in 4.3.2. Volunteers will have ample time to ask questions and discuss this study with NIH staff, and with their family, friends, and personal health care providers prior to signing the informed consent.

The informed consent process is conducted in person, with only relevant parties present, to protect the privacy of the subject. The study clinicians that are listed as Associate Investigators on the study are authorized to obtain consent and to respond to volunteers' questions as needed. Steps to reduce coercion or undue influence for volunteers who are NIH employees are described in the protocol 4.2.3.

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 scanned into the electronic medical record and a copy will be provided to the subject.

8.2. Risk/Benefit Assessment

8.2.1. Potential Risks

Risks of VRC01.23LS and mAb Administration

The side effects of mAbs are mild but may include reactions at the injection site (pain, redness, bruising, swelling), 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 [41]; however, this is not expected to be a risk for a mAb targeted to a viral antigen.

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 mAb targeted to human proteins or with the use of murine monoclonal antibodies which would have a risk of human anti-mouse antibodies [41]. It is expected that that VRC01.23LS

will have a low risk of such side effects since it is directed against a viral antigen and is human in origin.

Published experience with other human mAb directed against cell surface targets on lymphocytes have shown that infusion of a mAb may be associated with cytokine release, causing a reaction known as "cytokine release syndrome" (CRS) [42]. 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 when a non-human mAb, such as a murine mAb, is used [41]. Specifically, with regard to the rare CRS reactions, these generally occur within the first few hours of beginning the infusion and are more common 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, administration of histamine blockers, and restarting the infusion at a slower rate [43].

Delayed allergic reactions to other mAbs may include a serum sickness type of reaction, which is characterized by urticaria, fever, lymph node enlargement, and joint pains. These symptoms may not appear until several days after the exposure to the mAb and are noted to be more common with chimeric types of mAbs [41].

There are several FDA-licensed mAbs for which reactions related to the rate of IV infusion have been described. Some symptoms may be treated by slowing or stopping the infusion. Supportive treatment may also be indicated for some signs and symptoms.

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

Risks of Blood Drawing

Blood drawing may cause pain and bruising and may, infrequently, cause a feeling of lightheadedness or fainting. Rarely, it may cause infection at the site where the blood is taken. In this study, an IV line that can be used for the collection of blood may be left in place for several hours on the days when there are 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 (called phlebitis), or blood clot.

Risks of IV Infusions or SC Injections

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.

Risks of New Diagnoses

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

8.2.2 Assessment of Potential Risks and Benefits

The potential risks associated with participation of healthy volunteers in this study and receiving VRC01.23LS has been informed by results of previous VRC trials evaluating similar HIV mAbs with a favorable safety profile, as described in 1.2 and in the IB. In addition, a protocol specific risk management plan with a risk register has been established for this trial and assesses potential risks and strategies to mitigate risk, such as gradual initial enrollment in each dose group with a dose escalation plan (4.4) and study pause (4.5) and product discontinuation criteria (4.6) to minimize risk to subjects.

There are no direct benefits to study subjects from study participation. However, the study may benefit others as there is a potential benefit from knowledge gained in this study that would further inform the clinical development of HIV mAbs for the prevention or treatment of HIV infection.

8.3. Institutional Review Board

A copy of the protocol, informed consent form, other written subject information, and any advertising material will be submitted to the IRB for written approval.

The investigator must submit and 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 serious AEs 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

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the Sponsor(s) and their representatives. This confidentiality is extended to cover testing of biological samples and genetic tests 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 The Emmes Company, LLC, 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.

8.5. Certificate of Confidentiality

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.

8.6. Conflict of Interest

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

8.7. Plan for Use and Storage of Biological Samples

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

8.7.1. 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 study product 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 ICF. Genetic testing, including allotyping, may be done on collected specimens in an effort to evaluate for allotype-specific effects on pharmacokinetics.

8.7.2. 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 Vaccine Immunology Program laboratory (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).

8.7.3. 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. If the samples and/or data will be shared in an identified format, then IRB approval must be sought prior to any sharing of samples/data from this protocol. The research use of unlinked or de-identified samples are exempt from prospective IRB review and approval.

The samples will be stored in the VIP laboratory or in a VRC laboratory(ies). Data will be archived by the VRC in compliance with requirements for retention of research records.

8.7.4. Loss or Destruction of Samples, Specimens or Data

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

8.8. Subject Identification and Enrollment of Study Subjects

All study activities will be carried out at the NIH CC. Study subjects will be recruited through on-site and off-site advertising done for the 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 and will be limited to persons at least 18 years of age and no older than 60 years of age at enrollment.

8.9. 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 VRC designated Safety Officer for the day conducts 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 last product administration and will continue to monitor the safety data reports on a monthly basis 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, NIH IRB, Office of Human Research Protections, study PI, and FDA reserve the right to terminate the study. The PI will notify the IRB in writing of the study's completion or early termination.

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 IND Sponsor and regulatory authorities, as appropriate. If the study is prematurely terminated or suspended, the PI will promptly inform study participants, the 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 the 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
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the Sponsor, IRB, Office for Human Research Protections (OHRP), and, as applicable, the FDA.

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, microfiches, radiographs, 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 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. Clinical Monitoring, Data Collection and Data Sharing

9.3.1. Clinical Monitoring Plan

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 CRO. Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP 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.

9.3.2. Data Collection

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

9.3.3. Source Documents

The site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 GCP, regulatory and institutional requirements for the protection of confidentiality of subjects. Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, medical records, laboratory reports, pharmacy records and other research records maintained for the clinical trial.

9.3.4. 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 1 year of the primary completion date.

9.4 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 QC checks will be run on the database. Any missing data or data anomalies will be communicated to the site for clarification/resolution.

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

9.5. Language

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

9.6. 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 National Institutes of Health, the NIH CC, or the U.S. Federal Government will provide no long-term medical care or financial compensation for research-related injuries.

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APPENDIX I: SCHEDULE OF EVALUATIONS

Schedule 1: IV Group 1 (5 mg/kg), 3 (20 mg/kg), and 4 (40 mg/kg)																			
Visit Number		01	01R	02	02A	02B	02C	02D	02E	02F	03	04	05	06	07	08	11	12	13
Time After Infusion				Pre	EOI	1hr	2hr	4hr	24hr	48hr	Wk1	Wk2	Wk3	Wk4	Wk8	Wk12	Wk16	Wk20	Wk24
[1]Day of Study		-56 to -1	-42 to 0	D0	D0	D0	D0	D0	D1	D2	D7	D14	D21	D28	D56	D84	D112	D140	D168
Clinical	**Tube***	**Screen**	**Enroll**	**Day of Administration**															
VRC 500 Screening Consent		X																	
VRC 615 AoU; Consent			X																
[2]Physical examination		X	X	X	X				X	X	X	X	X	X	X	X	X	X	X
Complete medical history at screen; then interim med hx		X	X	X					X	X	X	X	X	X	X	X	X	X	X
[3]VRC01.23LS Administration				**X**															
Begin 7-day Diary Card				X															
CBC / differential	EDTA	3		3					3		3	3		3		3			
ALT, creatinine	GLT	4		4					4		4	4		4		4			
CMP: Total bili, BUN, albumin, protein, calcium, Na, K, Cl, CO_2, glucose, AST, ALP	GLT	X		X								X							
[4]Pregnancy Test: urine or serum		X	X	X								X					X		X
[4]Pregnancy Prevention Counseling		X	X	X								X					X		X
HIV Ab/Ag combo test	EDTA	3									3								
HIV Risk-Reduction Counseling		X		X							X								
Research Samples																			
PK	SST			4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
PBMCs	EDTA			20					20										
Serum	SST			24						8	8	8	8	8	8	8	8	8	8
Daily Volume (mL)		**10**	**0**	**55**	**4**	**4**	**4**	**4**	**31**	**12**	**22**	**19**	**12**	**19**	**12**	**19**	**12**	**12**	**12**
Cumulative Volume (mL)		**10**	**10**	**65**	**69**	**73**	**77**	**81**	**112**	**124**	**146**	**165**	**177**	**196**	**207**	**227**	**239**	**251**	**263**

Visit windows: Schedule visits 02A through 13 with respect to day 0:

Visit A (+10 min); Visits B and C (±10 min); Visit D (+2 hrs); Visits E, F (± 6 hrs); Visits 03, 04, 05, 06 (± 2 days), and Visits 07, 08, 11, 12, 13 (±7 days).

Not applicable to Schedule 1: Visits 02G, 09, 10

*Tube types and blood volumes are shown to meet current institutional requirements and projected blood volumes. Different tubes for clinical evaluations may be used to meet site requirements. Different volumes and tubes may be used for research blood samples when tubes as shown are not available, or as otherwise instructed by the IND Sponsor. Collected blood volumes will stay within the NIH CC blood draw limits for each subject.

[1]Day 0=day of first product administration. Day 0 is preferably scheduled within 14 days after enrollment but may be scheduled up to 42 days after enrollment to allow for the possibility of study pauses or scheduling difficulty with the approval of the PI. Day 0 evaluations prior to product administration are the baseline for assessing subsequent AEs.

(Footnotes continue to next page)

[2] Screening includes physical exam with vital signs (blood pressure, temperature, pulse, respiratory rate), height and weight. At other visits, if medically indicated, perform a targeted exam. Otherwise only vital signs are required, except at Visit 02 when the current weight is also obtained to use for ordering the study product, dosed based on "mg/kg."

[3] The PK blood draw "visits," defined by hours after an infusion, are relative to the exact time of the end of infusion (EOI). The exact start and end times of product administration and the time of PK blood draw(s) are recorded to ensure accurate PK analysis. In all IV groups, subjects will be observed in clinic for at least 2 hours following completion of product administration.

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

Schedule 2: SC Group 2 (5 mg/kg)																	
Visit Number		01	01R	02	02A	02E	02F	02G	03	04	05	06	07	08	11	12	13
Time After Infusion				Pre	EOI	24hr	48hr	72hr	Wk1	Wk2	Wk3	Wk4	Wk8	Wk12	Wk16	Wk20	Wk24
[1]Day of Study		-56 to -1	-42 to 0	D0	D0	D1	D2	D3	D7	D14	D21	D28	D56	D84	D112	D140	D168
Clinical	**Tube***	**Screen**	**Enroll**	**Day of Injection**													
VRC 500 Screening Consent		X															
VRC 615 AoU; Consent			X														
[2]Physical examination		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete medical history at screen; then interim med hx		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
[3]VRC01.23LS Administration				**X**													
Begin 7-day Diary Card				X													
CBC / differential	EDTA	3		3		3			3	3		3		3			
ALT, creatinine	GLT	4		4		4			4	4		4		4			
CMP: Total bili, BUN, albumin, protein, calcium, Na, K, Cl, CO_2, glucose, AST, ALP	GLT	X		X						X							
[4]Pregnancy test: urine or serum		X	X	X						X					X		X
[4]Pregnancy Prevention Counseling		X	X	X						X					X		X
HIV Ab/Ag combo test	EDTA	3							3								
HIV Risk-Reduction Counseling		X		X					X								
Research Samples																	
PK	SST			4		4	4	4	4	4	4	4	4	4	4	4	4
PBMCs	EDTA			20		20											
Serum	SST			24			8	8	8	8	8	8	8	8	8	8	8
Daily Volume (mL)		**10**	**0**	**55**	**0**	**31**	**12**	**12**	**22**	**19**	**12**	**19**	**12**	**19**	**12**	**12**	**12**
Cumulative Volume (mL)		**10**	**10**	**65**	**65**	**96**	**108**	**120**	**142**	**161**	**173**	**192**	**204**	**223**	**235**	**247**	**259**

Visit windows: Schedule visits 02A through 13 with respect to day 0:

Visit A (+10 min); Visits E, F, G (± 6 hrs.); Visits 03, 04, 05, 06 (± 2 days); Visits 07, 08, 11, 12, 13 (±7 days).

Not applicable to Schedule 2: Visits 02B, 02C, 02D, 09, 10

* Tube types and blood volumes are shown to meet current institutional requirements and projected blood volumes. Different tubes for clinical evaluations may be used to meet site requirements. Different volumes and tubes may be used for research blood samples when tubes as shown are not available, or as otherwise instructed by the IND Sponsor. Collected blood volumes will stay within the NIH CC blood draw limits for each subject.

[1] Day 0=day of first product administration. Day 0 is preferably scheduled within 14 days after enrollment but may be scheduled up to 42 days after enrollment to allow for the possibility of study pauses or scheduling difficulty with the approval of the PI. Day 0 evaluations prior to product administration are the baseline for assessing subsequent AEs.

(Footnotes continue to next page)

[2] Screening includes physical exam with vital signs (blood pressure, temperature, pulse, respiratory rate), height and weight. At other visits, if medically indicated, perform a targeted exam. Otherwise only vital signs are required, except at Visit 02 when the current weight is also obtained to use for ordering the study product, dosed based on "mg/kg."

[3] The PK blood draw "visits," defined by hours after an injection, are relative to the exact time of the end of injection (EOI). The exact start and end times of product administration and the time of PK blood draw(s) are recorded to ensure accurate PK analysis. In all SC groups, subjects will be observed for at least 1 hour after product administration.

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

Schedule 3: SC Group 5 (5 mg/kg by repeat dosing)																							
Visit Number		01	01R	02	02A	02E	02F	02G	03	04	06	07	08	08A	08E	08G	09	10	11	12	13	13A	13E
Time After Infusion				Pre D0	EOI D0	24hr	48hr	72hr	1wk	Wk2	Wk4	Wk8	Pre Wk12	EOI Wk12	24hr	72hr	Wk13	Wk14	Wk16	Wk20	Pre Wk24	EOI Wk24	24hr
[1]Day of Study		-56 to -1	-42 to 0	D0	D0	D1	D2	D3	D7	D14	D28	D56	D84	D84	D85	D87	D91	D98	D112	D140	D168	D168	D169
Clinical	**Tube***	**Screen**	**Enroll**	**Day of injection**									**Day of injection**								**Day of injection**		
VRC 500 Screening Consent		X																					
VRC 615 AoU; Consent			X																				
[2]Physical examination		X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	
Complete med history at screen; then interim med hx		X	X	X		X	X	X	X	X	X	X	X			X	X	X	X	X	X		
[3]VRC01.23LS Administration				X									X								X		
Begin 7-day Diary Card				X									X								X		
Phone contact; clinic visit if indicated															X								X
CBC / differential	EDTA	3		3		3			3	3	3		3			3	3	3	3		3		
ALT, creatinine	GLT	4		4		4			4	4	4		4			4	4	4	4		4		
CMP: Total bili, BUN, albumin, protein, calcium, Na, K, Cl, CO_2, glucose, AST, ALP	GLT	X		X						X			X					X			X		
[4]Pregnancy Test: urine or serum		X	X	X						X			X					X			X		
[4]Pregnancy Prevention Counseling		X	X	X						X			X					X			X		
HIV Ab/Ag combo test	EDTA	3							3								3						
HIV Risk-Reduction Counseling		X		X					X				X				X				X		
Research Samples																							
PK	SST			4		4	4	4	4	4	4	4	4			4	4	4	4	4	4		
PBMCs	EDTA			20		20																	
Serum	SST			24			8	8	8	8	8	8	8			8	8	8	8	8	8		
Daily Volume (mL)		**10**	**0**	**55**	**0**	**31**	**12**	**12**	**22**	**19**	**19**	**12**	**19**	**0**	**0**	**19**	**22**	**19**	**19**	**12**	**19**	**0**	**0**
Cumulative Volume (mL)		**10**	**10**	**65**	**65**	**96**	**108**	**120**	**142**	**161**	**180**	**192**	**211**	**211**	**211**	**230**	**252**	**271**	**290**	**302**	**321**	**321**	**321**

Visit windows: Schedule visits 02A through 08 with respect to day 0; visits 08A through 13 with respect to visit 08; visits 13A through 21 with respect to visit 13:

Visit A (+10 min); Visits 02E, 02F, 02G, 08G (± 6 hrs.); Visits 08E, 13E (+ 1 day); Visits 03, 04, 09, 10 (± 2 days); Visits 06, 07, 08, 11, 12, 13 (± 7 days, with not less than 21 days between injections).

Not applicable to Schedule 3: Visits B, C, D, 05

*Tube types and blood volumes are shown to meet current institutional requirements and projected blood volumes. Different tubes for clinical evaluations may be used to meet site requirements. Different volumes and tubes may be used for research blood samples when tubes as shown are not available, or as otherwise instructed by the IND Sponsor. Collected blood volumes will stay within the NIH CC blood draw limits for each subject.

[1]Day 0=day of first product administration. Day 0 is preferably scheduled within 14 days after enrollment but may be scheduled up to 42 days after enrollment to allow for the possibility of study pauses or scheduling difficulty with the approval of the PI. Day 0 evaluations prior to product administration are the baseline for assessing subsequent AEs. *(Footnotes continue to next page)*

[2] Screening includes physical exam with vital signs (blood pressure, temperature, pulse, respiratory rate), height and weight. At other visits, if medically indicated, perform a targeted exam. Otherwise only vital signs are required, except at all product administration visits (02, 08, 13) when the current weight is also obtained to use for ordering the study product, dosed based on "mg/kg."

[3] The PK blood draw "visits," defined by hours after an injection, are relative to the exact time of the end of injection (EOI). The exact start and end times of product administration and the time of PK blood draw(s) are recorded to ensure accurate PK analysis. In all SC groups, subjects will be observed for at least 1 hour after product administration.

[4] Pregnancy test results must be negative before each study product administration. Complete a Pregnancy Prevention Form when pregnancy test is given.

*The study schedule for subjects who discontinue product administration will be modified as follows:

- Subjects who receive only one product administration will follow Schedule 3 through Visit 07, and then move to Schedule 5.
- Subjects who receive two product administrations will follow Schedule 3 through Visit 12 and then move to Schedule 5.

Schedule 3 (continued): SC Group 5 (5 mg/kg by repeat dosing)										
Visit Number*		13G	14	15	16	17	18	19	20	21
Time After Infusion		72 hr	Wk25	Wk26	Wk28	Wk32	Wk36	Wk40	Wk44	Wk48
Day of Study		D171	D175	D182	D196	D224	D252	D280	D308	D336
Clinical	**Tube^**									
Physical examination if medically indicated, otherwise only vitals		X	X	X	X	X	X	X	X	X
Interim medical history		X	X	X	X	X	X	X	X	X
CBC / differential	EDTA	3	3	3	3					
ALT, creatinine	GLT	4	4	4	4					
CMP: Total bili, BUN, albumin, protein, calcium, Na, K, Cl, CO_2, glucose, AST, ALP	GLT			X						
[1]Pregnancy test: urine or serum				X			X			X
[1]Pregnancy Prevention Counseling				X			X			X
HIV Ab/Ag combo test	EDTA		3							
HIV risk-reduction counseling			X							
Research Samples										
PK samples	SST	4	4	4	4	4	4	4	4	4
Serum	SST	8	8	8	8	8	8	8	8	8
Daily Volume (mL)		**19**	**22**	**19**	**19**	**19**	**12**	**12**	**12**	**12**
Cumulative Volume (mL)		**340**	**362**	**381**	**400**	**412**	**424**	**436**	**448**	**460**

Visit windows: Schedule visits 13G through 21 with respect to visit 13.

Visit 13G (± 6 hrs), Visits 14-17 (±2 days), and Visits 18-21 (±7 days).

[1] Complete a Pregnancy Prevention Form when pregnancy test is given.

*The study schedule for subjects who discontinue product administration will be modified as follows:

- Subjects who have only received one product administration will follow Schedule 3 through Visit 07, and then move to Schedule 5.
- Subjects who have received two product administrations will follow Schedule 3 through Visit 12 and then move to Schedule 5.

Schedule 4: IV Group 6 (20 mg/kg by repeat dosing)																										
Visit Number		01	01R	02	02A	02B	02C	02D	02E	02F	03	04	06	07	08	08A	08B	08E	08F	09	10	11	12	13	13A	13B
Time After Infusion				Pre D0	EOI D0	1hr	2hr	4hr	24hr	48h	Wk1	Wk2	Wk4	Wk8	Pre Wk12	EOI Wk12	1hr	24hr	48hr	Wk13	Wk14	Wk16	Wk20	Pre Wk24	EOI Wk24	1hr
[1]Day of Study		-56 to -1	-42 to 0	D0	D0	D0	D0	D0	D1	D2	D7	D14	D28	D56	D84	D84	D84	D85	D86	D91	D98	D112	D140	D168	D168	D168
Clinical	**Tube***	**Screen**	**Enroll**	**Day of infusion**											**Day of infusion**									**Day of infusion**		
VRC 500 Screening Consent		X																								
VRC 615 AoU; Consent			X																							
[2]Physical examination		X	X	X	X				X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	
Complete med history at screen; then interim med hx		X	X	X					X	X	X	X	X	X	X				X	X	X	X	X	X		
[3]VRC01.23LS Administration				X											X									X		
Begin 7-day Diary Card				X											X									X		
Phone contact; clinic visit if indicated																		X								
CBC / differential	EDTA	3		3					3		3	3	3		3				3	3	3	3		3		
ALT, creatinine	GLT	4		4					4		4	4	4		4				4	4	4	4		4		
CMP: Total bili, BUN, albumin, protein, calcium, Na, K, Cl, CO_2, glucose, AST, ALP	GLT	X		X								X			X						X			X		
[4]Pregnancy Test: urine or serum		X	X	X								X			X						X			X		
[4]Pregnancy Prevention Counseling		X	X	X								X			X						X			X		
HIV Ab/Ag combo test	EDTA	3									3									3						
HIV Risk-Reduction Counseling		X		X							X				X					X				X		
Research Samples																										
PK	SST			4	4	4	4	4	4	4	4	4	4	4	4	4	4		4	4	4	4	4	4	4	4
PBMCs	EDTA			20					20																	
Serum	SST			24						8	8	8	8	8	8				8	8	8	8	8	8		
Daily Volume (mL)		**10**	**0**	**55**	**4**	**4**	**4**	**4**	**31**	**12**	**22**	**19**	**19**	**12**	**19**	**4**	**4**	**0**	**19**	**22**	**19**	**19**	**12**	**19**	**4**	**4**
Cumulative Volume (mL)		**10**	**10**	**65**	**69**	**73**	**77**	**81**	**112**	**124**	**146**	**165**	**184**	**196**	**215**	**219**	**223**	**223**	**242**	**264**	**283**	**302**	**314**	**333**	**337**	**341**

Visit windows: Schedule visits 02A through 08 with respect to Day 0; visits 08A through 13 with respect to Visit 08.

Visits A (+10 min); Visits B and C (±10 min); Visit D (+2 hrs.); Visits 02E, 02F (± 6 hrs.); Visit 08E (+1 day), Visit 08F (+ 2 days), Visits 03, 04, 09, 10 (± 2 days); Visits 06, 07, 08, 11, 12, 13 (±7 days, with not less than 21 days between infusions).

Not applicable to Schedule 4: Visit G, 05, 08C, 08D, 08G, 13B, 13C, 13D

*Tube types and blood volumes are shown to meet current institutional requirements and projected blood volumes. Different tubes for clinical evaluations may be used to meet site requirements. Different volumes and tubes may be used for research blood samples when tubes as shown are not available, or as otherwise instructed by the IND Sponsor. Collected blood volumes will stay within the NIH CC blood draw limits for each subject. *(Footnotes continue to next page)*

[1] Day 0=day of first product administration. Day 0 is preferably scheduled within 14 days after enrollment but may be scheduled up to 42 days after enrollment to allow for the possibility of study pauses or scheduling difficulty with the approval of the PI. Day 0 evaluations prior to product administration are the baseline for assessing subsequent AEs.

[2] Screening includes physical exam with vital signs (blood pressure, temperature, pulse, respiratory rate), height and weight. At other visits, if medically indicated, perform a targeted exam. Otherwise only vital signs are required, except at all product administration visits (02, 08, 13) when the current weight is also obtained to use for ordering the study product, dosed based on "mg/kg."

[3] The PK blood draw "visits," defined by hours after an infusion, are relative to the exact time of the end of infusion. Exact start and end times of product administration and the time of PK blood draw(s) are recorded to ensure accurate PK analysis. In all IV groups, subjects will be observed for at least 2 hours after the product administration.

[4] Pregnancy test results must be negative for women of reproductive potential before each product administration. Complete a Pregnancy Prevention Form when pregnancy test given.

**The study schedule for subjects who discontinue product administration will be modified as follows:

- Subjects who receive only one product administration will follow Schedule 4 through Visit 07, and then move to Schedule 5.
- Subjects who receive two product administrations will follow Schedule 4 through Visit 12 and then move to Schedule 5.

Schedule 4 (continued): IV Group 6 (20 mg/kg by repeat dosing)											
Visit Number*		13E	13F	14	15	16	17	18	19	20	21
Time After Infusion		24hr	48hr	Wk25	Wk26	Wk28	Wk32	Wk36	Wk40	Wk44	Wk48
Day of Study		D169	D170	D175	D182	D196	D224	D252	D280	D308	D336
Clinical	**Tube**										
Physical examination if medically indicated, otherwise only vitals			X	X	X	X	X	X	X	X	X
Interim medical history			X	X	X	X	X	X	X	X	X
Phone contact; clinic visit if indicated		X									
CBC / differential	EDTA		3	3	3	3					
ALT, creatinine	GLT		4	4	4	4					
CMP: Total bili, BUN, albumin, protein, calcium, Na, K, Cl, CO2, glucose, AST, ALP	GLT				X						
Pregnancy Test: urine or serum					X			X			X
Pregnancy Prevention Counseling when pregnancy test given					X			X			X
HIV Ab/Ag combo test	EDTA			3							
HIV Risk-Reduction Counseling				X							
Research Samples											
PK	SST		4	4	4	4	4	4	4	4	4
Serum	SST		8	8	8	8	8	8	8	8	8
Daily Volume (mL)		**0**	**19**	**22**	**19**	**19**	**12**	**12**	**12**	**12**	**12**
Cumulative Volume (mL)		**341**	**360**	**382**	**401**	**420**	**432**	**444**	**456**	**468**	**480**

Visit windows: Schedule visits 13E through 21 with respect to visit 13.

Visit 13E (+1 day); Visit 13F (+2 days), Visits 14-17 (±2 days), and Visits 18-21 (±7 days).

* The study schedule study schedule for subjects who discontinue product administration will be modified as follows:

- Subjects who receive only one product administration will follow Schedule 4 through Visit 7, and then move to Schedule 5.
- Subjects who receive two product administrations will follow Schedule 4 through Visit 12 and then move to Schedule 5.

Schedule 5: For Subjects in Groups 5 and 6 Discontinued from Further Product Administration(s)								
Visit Number		08	11	12	13	16	17	18
Time After Infusion		Wk12	Wk16	Wk20	Wk24	Wk28	Wk32	Wk36
Day of Study		D84	D112	D140	D168	D196	D224	D252
Clinical	**Tube***							
Physical examination if medically indicated, otherwise only vitals		X	X	X	X	X	X	X
Interim medical history		X	X	X	X	X	X	X
Pregnancy Test: urine or serum			X		X			X
Pregnancy Prevention Counseling when pregnancy test given			X		X			X
Research Samples								
PK	SST	4	4	4	4	4	4	4
Serum	SST	8	8	8	8	8	8	8
Daily Volume (mL)		**12**	**12**	**12**	**12**	**12**	**12**	**12**
If starting at Visit 8	**Cumulative Volume (mL), Group 5**		**211**	**223**	**235**	**247**		
	Cumulative Volume (mL), Group 6		**215**	**227**	**239**	**251**		
If starting at Visit 13	**Cumulative Volume (mL), Group 5**					**321**	**333**	**345**	**357**
	Cumulative Volume (mL), Group 6					**333**	**345**	**357**	**369**

Visit windows: ±7 days for all visits shown.

*Tube types and blood volumes are shown to meet current institutional requirements and projected blood volumes. Different tubes for clinical evaluations may be used to meet site requirements. Different volumes and tubes may be used for research blood samples when tubes as shown are not available, or as otherwise instructed by the IND Sponsor. Collected blood volumes will stay within the NIH CC blood draw limits for each subject.

Group 5 or 6 subjects who do not receive the 2nd or 3rd product administrations will continue participation under this modified schedule:

- If only one product administration received, subjects will follow their originally assigned study schedule through Visit 7 and then move to Schedule 5 for Visits 8-13. Their final study visit will be Visit 13.
- If two product administrations received, subjects will follow their originally assigned study schedule through Visit 12 and then move to Schedule 5 for Visits 13-18. Their final study visit will be Visit 18.

APPENDIX II: ASSESSMENT OF RELATIONSHIP TO STUDY PRODUCT AND TABLE FOR GRADING SEVERITY OF ADVERSE EVENTS

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

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

- **Definitely Related**. The AE and administration of study product are related in time, and a direct association can be demonstrated.
- **Probably Related**. The AE and administration of study product are reasonably related in time, and the AE is more likely explained by study product than other causes.
- **Possibly Related**. The AE and administration of study product are reasonably related in time, but the AE can be explained equally well by causes other than study product.
- **Not Related**. There is not a reasonable possibility that the AE is related to the study product.

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

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

Table for Grading Severity of Adverse Events:

For consistency with other studies of VRC mAb products, the U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1. [July 2017]. Available from:

https://rsc.tech-res.com/docs/default-source/safety/division-of-aids-(daids)-table-for-grading-the-severity-of-adult-and-pediatric-adverse-events-corrected-v-2-1.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 adverse events 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 greater.