Official Title: A Phase 1 Dose-Escalation Study of the Safety and Pharmacokinetics of a Human Monoclonal Antibody, VRC-HIVMAB075-00-AB (VRC07-523LS), Administered Intravenously or Subcutaneously to Healthy Adults

ClinicalTrials.gov Identifier: NCT03015181

Document Type:

- Redacted Study Protocol (Statistical Analysis Considerations located in Section 6 of the Protocol 4.0)
- Redacted IRB-approved Informed Consent (final version)

Document/Date:

- Protocol Version 4.0: October 11, 2017
- IRB-approved Informed Consent Version 3.0: August 15, 2017

Version 4.0
October 11, 2017

VACCINE RESEARCH CENTER

Protocol VRC 605
(NIH 17-I-0030)

A PHASE 1 DOSE-ESCALATION STUDY OF THE SAFETY AND PHARMACOKINETICS OF A HUMAN MONOCLONAL ANTIBODY, VRC-HIVMAB075-00-AB (VRC07-523LS), ADMINISTERED INTRAVENOUSLY OR SUBCUTANEOUSLY TO HEALTHY ADULTS

Study Product Provided by
Vaccine Research Center/NIAID/NIH, Bethesda, MD

Clinical Trial Sponsored by:
National Institute of Allergy and Infectious Diseases (NIAID)
Vaccine Research Center (VRC)
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IND Sponsored by:
National Institute of Allergy and Infectious Diseases
Vaccine Research Center (VRC)
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IND 133,027

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IRB Initial Review Date: November 21, 2016

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ABBREVIATIONS

Abbreviation	Term
ADA	anti-drug antibody
AE	adverse event
AIDS	Acquired Immunodeficiency Syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AoU	Assessment of Understanding
ART	antiretroviral therapy
AST	aspartate aminotransferase
AUC	area under the curve
β-HCG	human chorionic gonadotropin
BMI	body mass index
BUN	blood urea nitrogen
CBC	complete blood count
Cmax	maximum concentration
CRS	cytokine release syndrome
cGMP	current Good Manufacturing Practice
DAIDS	Division of AIDS
EDTA	Ethylenediaminetetraacetate
ELISA	enzyme-linked immunosorbent assay
Env	Envelope
EOI	end of infusion
F	Bioavailability
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GLT	(green) lithium heparin tube
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HRPP	Human Research Protections Program
IB	Investigator's Brochure
ICF	informed consent form
IgG1	Immunoglobulin G1
IND	investigational new drug application
IRB	Institutional Review Board
IV	Intravenous
kg	Kilogram
L	Liter
LIMS	Laboratory Information Management System
λz	terminal slope of concentration vs time profile
MAb	monoclonal antibody
mcg	Microgram

Abbreviation	Term
mg	Milligram
mL	Milliliter
mM, mmol	Millimole
MSD	Meso Scale Discovery
MTCT	mother-to-child transmission
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NIH CC	National Institutes of Health Clinical Center
NHP	Non-human primate
NVITAL	NIAID Vaccine Immune T-Cell and Antibody Laboratory
OHRP	Office for Human Research Protections
PBMC	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PI	Principal Investigator
PK	Pharmacokinetic
PSRT	Protocol Safety Review Team
Q	Inter-compartmental clearance
QA	quality assurance
RSC	Regulatory Support Center
SAE	serious adverse event
SC	Subcutaneous
SHIV	simian-human immunodeficiency virus
SST	serum separator tube
TCR	tissue cross reactivity
$T_{½}$	half-life
Tmax	time of maximal concentration (Cmax)
UNAIDS	Joint United Nations Programme on HIV/AIDS
UP	unanticipated problem
USP	United States Pharmacopeia
Vd	volume of distribution
VRC	Vaccine Research Center
WBC	white blood cell

PRÉCIS

VRC 605: A Phase 1 Dose-Escalation Study of the Safety and Pharmacokinetics of a Human Monoclonal Antibody, VRC-HIVMAB075-00-AB (VRC07-523LS), Administered Intravenously or Subcutaneously to Healthy Adults

Study Design: This is the first study in healthy adults of the VRC-HIVMAB075-00-AB (VRC07-523LS) monoclonal antibody (MAb). It is a dose-escalation study to examine safety, tolerability, dose, and pharmacokinetics of VRC07-523LS. The hypothesis is that VRC07-523LS administration to healthy adults will be safe by the intravenous (IV) and subcutaneous (SC) routes. A secondary hypothesis is that VRC07-523LS will be detectable in human sera with a definable half-life.

Product Description: VRC-HIVMAB075-00-AB (VRC07-523LS) is a human MAb targeted to the HIV-1 CD4 binding site. It was developed by the VRC/NIAID/NIH and manufactured under current Good Manufacturing Practice regulations at the VRC Pilot Plant operated under contract by the Vaccine Clinical Materials Program, Leidos Biomedical Research, Inc., Frederick, MD. Product is provided at 100 ± 10 mg/mL in a volume of 6.25 ± 0.10 mL filled into 10 mL glass vials.

Subjects: Healthy adults, 18-50 years of age.

Study Plan: This study includes 4 open-label, dose escalations of VRC07-523LS from 1 mg/kg IV to 40 mg/kg IV, 1 route escalation from IV to SC, and 2 open-label groups to assess repeat dosing of VRC07-523LS. Groups will be enrolled per the dose and route escalation and safety evaluation plan.

VRC 605 Study Schema

Group	Subjects	Administration Schedule		
		Day 0	Week 12	Week 24
1	3	1 mg/kg IV		
2	3	5 mg/kg IV		
3	3	5 mg/kg SC		
4	3	20 mg/kg IV		
5	3	40 mg/kg IV		
6	5	5 mg/kg SC	5 mg/kg SC	5 mg/kg SC
7	5	20 mg/kg IV	20 mg/kg IV	20 mg/kg IV
Total*	25	*The expected enrollment is 25 subjects. Enrollment up to a total of 40 subjects is permitted if additional subjects are necessary for safety or PK evaluations.		

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

1. INTRODUCTION

The global incidence of new human immunodeficiency virus (HIV) infection peaked in the mid-1990s. The incidence of new infections in 2014 is reported by Joint United Nations Programme on HIV/AIDS (UNAIDS) as 2 million new cases, a reduction of 35% since 2000, with an estimated global total of 36.9 million people living with HIV [1]. The decrease in HIV incidence, due to multiple factors including prevention and treatment programs, is an encouraging trend but the scope and cost of the epidemic remains a global health threat.

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 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].

The VRC, NIAID, NIH has developed VRC07-523LS, a highly potent and broadly neutralizing HIV-1 human MAb targeted against the HIV-1 CD4 binding site. A similar antibody, VRC01 MAb, is currently in clinical trials under IND 113,611 [prevention indication] and IND 126,001 and IND 126,664 [therapeutic indication], was originally discovered in a subject infected with HIV-1 for more than 15 years and whose immune system controlled the virus without anti-retroviral therapy [5]. Through advances in B-cell immunology, cloning and structure-guided optimization techniques, numerous HIV-1 neutralizing MAbs, including VRC07 ("07" denotes sequential numbering when discovered), VRC07-523 ("523" denotes sequential numbering when engineered variant generated), and later VRC07-523LS ("LS" denotes 2 amino acid mutations), were isolated with potency and breadth greater than those of early antibodies[3].

The VRC07 (wild-type) heavy chain was identified by 454 deep sequencing based on its similarity to the VRC01 MAb and paired with the VRC01 (wild-type) light chain. The mutations that together define the 523 designations are a glycine to histidine mutation at residue 54 of the heavy chain, a deletion of the first two amino acids, glutamate and isoleucine, from the light chain, and a valine to serine mutation at the third amino acid residue of the light chain. The LS designation specifies methionine to leucine (L) and asparagine to serine (S) (M428L/N434S, referred to as LS) changes within the C-terminus of the heavy chain constant region. The LS mutation was introduced by site-directed mutagenesis to increase the binding affinity for the neonatal Fc-receptor (FcRn), resulting in increased recirculation of functional IgG [6, 7], thus increasing plasma half-life.

VRC-HIVMAB075-00-AB (VRC07-523LS) is an investigational drug that has not been administered to humans prior to this study. VRC07-523LS is intended for the prevention of HIV-1 infection in healthy adults initially. VRC07-523LS may also be evaluated for prevention of mother-to-child transmission and for treatment of HIV-1 infected subjects.

1.1 RATIONALE FOR THE STUDY

VRC's clinical development plans for neutralizing MAbs include potential uses in three broad areas: 1) prevention of mother-to-child transmission (MTCT) of HIV, 2) prevention of sexual transmission of HIV, and 3) therapeutic application in HIV-1 infected individuals. The initial development plan focused on clinical research to lead to an efficacy evaluation of VRC01 for MTCT of HIV. To evaluate the safety of administering VRC01 to infants who may be HIV-infected at birth, studies in infants were preceded by Phase 1 trials in HIV-infected adults (VRC 601) and HIV-uninfected adults (VRC 602) that began in 2013 and 2014, respectively.

VRC01 has been assessed as safe and well tolerated at the 5-40 mg/kg doses administered intravenously (IV) and at 5 mg/kg subcutaneously (SC) in both HIV-infected and HIV-uninfected adult populations. The pharmacokinetic (PK) parameters of passively administered VRC01 were also evaluated. For healthy adults who received VRC01 at the 5-40 mg/kg doses administered IV (n=18), the clearance was 0.016±0.003 L/h and an overall mean value for the elimination half-life was 15.4±3.9 days for IV administration. At 5 mg/kg SC (n=5), the clearance was 0.029±0.007 L/h, and the mean elimination half-life was 16.6 ± 2.9 days. Work is ongoing to further describe the PK and biological activity of VRC01 after repeat dosing in HIV-infected and -uninfected adults.

VRC07-523LS, an engineered variant of VRC07 that was discovered in the same HIV-1 infected subject as VRC01, neutralizes more HIV envelope strains than VRC01 at lower concentrations.

VRC07-523LS was found to be 5-to 8-fold more potent than VRC01, with an inhibitory concentration IC_{50} <50 mcg/mL against 96% of HIV-1 pseudoviruses representing the major circulating HIV-1 clades and IC_{50} <1 mcg/mL against 92% of HIV-1 viruses tested and displayed minimal levels of autoreactivity. VRC07-523LS was shown to have a prolonged half-life over VRC07 by about 2-fold [3].

In vivo proof-of-concept studies showed that VRC07-523LS is about 5-fold more potent than VRC01LS in Rhesus macaques and displays a longer half-life (9.8 days) than VRC07 (4.9 days) after a single dose of MAb at 10 mg/kg administered IV [3].

When administered IV at a single dose of 10 mg/kg in cynomolgus macaques, the half-life of VRC07-523LS was about 12 days, and persisted at least 28 days (last collection point) in rectal and vaginal secretions and tissues. When administered SC at a single dose of 10 mg/kg in rhesus macaques, the half-life of VRC07-523LS was about 14 days and it persisted at least 49 days (last collection point) in rectal, vaginal and nasal secretions. Complete protection from SHIV-SF162P3 challenge was demonstrated with a single dose of VRC07-523LS at 20 mg/kg administered IV.

A repeat dose IV and SC toxicity study with VRC07-523LS was performed in male and female Sprague-Dawley rats in accordance with "Good Laboratory Practice (GLP) for Nonclinical Laboratory Studies." Treatment with VRC07-523LS at doses up to 400 mg/kg/dose IV or 40 mg/kg/dose SC with three doses at 10 days intervals was generally well tolerated as most findings were reversible and no longer seen at the end of the recovery period. Additionally, histologic changes were not observed in the GLP repeat dose toxicology study in the cell types with staining observed in the GLP tissue cross reactivity (TCR) study.

Increased neutralization potency *in vitro* and prolonged half-life of VRC07-523LS correlate with improved protection against SHIV infection *in vivo* in animal studies, suggesting a potential clinical application against HIV-1 infection in humans in preventive and/or therapeutic settings.

The proposed VRC07-523LS doses are based on human studies of VRC01, preclinical studies of VRC07-523LS and the requirements to assess PK at a range of doses that will allow for full PK analysis and predictive modeling. This range of doses allows for informative PK modeling to be performed with the study data obtained here. Preclinical studies with VRC07-523LS to date also support the proposed human doses and intervals between doses to achieve passive immunity as described in Section 2 and in the Investigator's Brochure (IB).

1.2 VRC07-523LS SPECIFIC LABORATORY ASSESSMENTS

Laboratory assessments in this Phase 1 study of VRC07-523LS include PK parameters, development of anti-VRC07-523LS antibody following exposure to the product, and functional capacity (neutralization) of the MAb following infusion.

VRC07-523LS concentration for the PK analysis in this Phase 1 study will be measured by an ELISA on a Beckman Biomek based automation platform. The monoclonal antibody 5C9 is coated onto Immulon-4HXB microtiter plates overnight at 4° C at a concentration of 3.5 mg/mL. Plates are washed and blocked (10% FBS in PBS) for 2 hours at room temperature. Duplicate serial 3-fold dilutions covering the range of 100 - 24300 of the test sample are incubated 2 hours at 37° C followed by Horseradish Peroxidase - labeled goat anti-human antibody (1hour, 37° C), and TMB substrate (15 minutes, room temperature). Color development is stopped by addition of sulfuric acid and plates are read within 30 minutes at 450 nm via the Molecular Devices Paradigm plate reader. Four parameter logistic curve regression of a standard curve of VRC07-523LS covering the range from 0.98 to 1000 ng/mL is utilized to quantitate the sample concentrations based upon the average of sample dilutions within the range of the assay.

Assessment for development of anti-VRC07-523LS antibodies in subjects will be performed using the Meso Scale Discovery (MSD) platform based on electrochemiluminescence. The developed ADA assay uses the biotin-labeled VRC07 immobilized on a streptavidin-coated MSD plate as the capture molecule, and the SULFO-TAG labeled VRC07 as the reporter molecule. This assay is independent of the anti-VRC07-523LS antibody isotype, and permits the detection of both high and low affinity antibodies. Evaluation for anti-VRC07-523LS antibodies will be conducted in batches, on samples collected at 4 weeks after each antibody administration. Samples collected at other visits could be tested if there is a clinical indication or a decrease in PK values observed.

Depending upon the concentrations measured in collected specimens, further evaluation of the research samples to assess for functional capacity to neutralize HIV may be conducted by an *in vitro* cell-based virus neutralization assay using the pseudotyped viruses [8-10].

As an exploratory evaluation, subjects may be evaluated for their IgG1 allotypes to determine the potential for theoretical allotype-specific effects on the VRC07-523LS pharmacokinetics such as reduced half-life or anti-drug antibody response [11-13]. Coded stored samples will be used for evaluation of the genetic sequence of the immunoglobulin heavy chain constant region allotype.

1.3 PREVIOUS HUMAN EXPERIENCE

There is no previous human experience with VRC07-523LS administration. VRC01 and its variant VRC01LS are similar products and previous human experience related to VRC01 and VRC01LS is described here.

1.3.1 VRC01 Safety Data

Evaluation of VRC01 as an investigational drug began in humans in September 2013. Initial development of VRC01 was based on an intended indication for the prevention of HIV-1 infection in infants at risk for HIV-1 infection through maternal transmission at birth or during breastfeeding. Further evaluation of VRC01 in adults and infants for preventative and therapeutic indication is ongoing in phase 1 and phase 2 trials.

Overall, as of January 10, 2017, VRC01 administration in the dose range from 1 to 40 mg/kg IV and at 5 and 40 mg/kg SC have been assessed as well-tolerated in adults and infants and safe for further evaluation. Cumulatively, across all studies, VRC01 has been administered to over 840 HIV-uninfected and HIV-infected adults and 33 HIV uninfected infants. There have been no SAEs related to VRC01 that required expedited reporting to the FDA or other regulatory authorities and no study safety pauses for adverse events. A non-serious AE of urticaria was submitted to regulatory authorities as a safety report because urticaria, at the grade 3 severity, was not reported in the IB (Version 6.0 dated October 5, 2016)

1.3.2 VRC01LS Safety Data

VRC01LS began evaluation in HIV-uninfected adults in the VRC 606 study in November 2015. Evaluation of VRC01LS in HIV-infected adults in the VRC 607 study was initiated in April 2017. There have been no SAEs reported in VRC 606 as of July 17, 2017. Overall 29 of 39 (74.4%) subjects who began product administrations have had one or more unsolicited AEs, with a maximum severity being Grade 1 for 18 subjects and Grade 2 for 11 subjects.

VRC01LS administrations have been generally well tolerated. Overall, 3 of 21 subjects (14.3%) who received VRC01LS IV and 14 of 18 subjects (77.8%) who received VRC01LS SC reported solicited local reactions in the week after product administration. The most frequent local reaction was pain/tenderness at injection site reported by 14 subjects (2 for IV and 12 for SC administration) at a maximum severity being mild, and being moderate by 1 subject for SC product administration. Other local reactogenicity symptoms included mild bruising (n=1), swelling (n=2), and redness (n=2).

With regard to solicited systemic adverse events, 13 of 39 subjects (33.3 %) had one or more mild systemic signs or symptoms reported in the 3 days after product administration. This included mild malaise (n=10), myalgia (n=6), headache (n=4), and nausea (n=4).

Observations during product administration included brief reactions of local pain and/or stinging sensations at SC administration sites (15 of 18 subjects, 83.3%) that resolved within 2-5 minutes after injection. These reactions were consistent with known risks of injections and did not meet criteria for reporting as AEs as defined by the Table for Grading Severity of Adverse Events. No systemic symptoms were reported during product administration.

As of 7/17/2017, no local or systemic reactogenicity were reported during VRC01LS administrations in VRC 607 study in HIV-infected adults; all infusions were completed as per protocol. All 4 subjects reported maximal solicited local reactogenicity as “none” on a 3-day diary card. As to systemic solicited reactogenicity, one subject reported mild symptoms of headache, chills, and nausea that resolved within 7-11 days after product administration. No SAEs were reported; all unsolicited AEs were Grade 1 (mild) or Grade 2 (moderate), and assessed as unrelated to study product.

1.3.3 VRC07-523LS Safety Data

As of July 17, 2017, 9 out of 10 subjects enrolled in VRC 605 have received at least one dose of VRC07-523LS (7 IV administrations and 1 SC administration). One subject withdrew from the study due to time commitment and did not receive study product. There have been no SAEs and no

study safety pauses for adverse events (AEs), with maximum severity being Grade 1 for 3 subjects and Grade 2 for 1 subject. None of the AEs were related to study product.

For solicited local reactions in the week after VRC07-523LS IV administrations, one subject reported mild bruising. There were no local reactions reported by the one subject that received VRC07-523LS subcutaneously. With regard to solicited systemic events, one subject who received VRC07-523L via IV route reported mild myalgia.

The final PSRT review occurred on August 9, 2017(Section 4.3). After each review, the PSRT concluded that product administrations were well tolerated and to proceed with the next dose and/or route escalation. Repeat dosing was recommended for subjects enrolled in Groups 6 and 7.

1.4 PHARMACOKINETIC PARAMETERS

The PK parameters of the passively administered, similar MAb VRC01 have been evaluated in healthy and HIV-infected adults and can be found in published studies [14, 15] and the IB. Work is ongoing to further describe the PK of VRC01 by the IV and SC routes of administration after a single dose and a repeat dosing in adults. The PK parameters of VRC07-523LS in humans will be evaluated in this study.

2. STUDY PRODUCT

The study product, VRC-HIVMAB075-00-AB (VRC07-523LS) was produced under current Good Manufacturing Practice (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. Specific manufacturing information is included on the product vial label and in the IB. Quality Assurance (QA) lot release testing by the manufacturer and ongoing stability programs verify conformance to product specifications throughout use in clinical trials.

2.1 VRC-HIVMAB075-00-AB

VRC-HIVMAB075-00-AB (VRC07-523LS) is a broadly neutralizing human MAb targeted against the HIV-1 CD4 binding site. It was developed by VRC/NIAID/NIH. Generation and testing of VRC07-523LS is briefly described. The VRC07 (wild-type) heavy chain was identified by 454 deep sequencing based on its similarity to the VRC01 MAb and paired with the VRC01 (wild-type) light chain. The mutations that together define the 523 designations are a glycine to histidine mutation at residue 54 of the heavy chain, a deletion of the first two amino acids, glutamate and isoleucine, from the light chain, and a valine to serine mutation at the third amino acid residue of the light chain. The LS designation specifies methionine to leucine (L) and asparagine to serine (S) (M428L/N434S, referred to as LS) changes within the C-terminus of the heavy chain constant region. The LS mutation was introduced by site-directed mutagenesis to increase the binding affinity for the neonatal Fc-receptor (FcRn), resulting in increased recirculation of functional IgG, thus increasing plasma half-life.

The bulk lot of the drug substance was manufactured under cGMP using a stably transfected Chinese Hamster Ovary (CHO) DG44 cell line and purified. The drug product was filled into glass vials and labeled at the VRC Pilot Plant. Each 10 mL glass vial contains 6.25 ± 0.10 mL at a concentration of 100 mg/mL ± 10 mg/mL of VRC07-523LS in formulation buffer consisting of 50 mM Histidine, 50 mM Sodium Chloride, 5% Sucrose, and 2.5% Sorbitol at pH 6.8.

More details on VRC-HIVMAB075-00-AB composition and manufacturing are found in the IB.

2.2 PRECLINICAL TOXICOLOGY STUDY

A repeat dose IV and SC toxicity and pharmacokinetic study of clinical-grade VRC-HIVMAB075-00-AB (VRC07-523LS) in male and female Sprague-Dawley rats was performed by IITRI, Chicago, IL in accordance with Good Laboratory Practice (GLP) regulations. Treatment with VRC-HIVMAB075-00-AB (VRC07-523LS), at doses up to 400 mg/kg/dose IV or 40 mg/kg/dose SC with three doses at 10-day intervals, was well-tolerated as most findings were reversible and no longer seen at the end of the recovery period. Refer to the IB for more information about this study.

2.3 *IN VITRO* SAFETY STUDIES

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

Table 1: *In Vitro* Preclinical Safety Studies

Study Purpose	Study Outcome
Assessment of anti-phospholipid reactivity	VRC07-523LS has slight reactivity to phospholipids [3]
Assessment of anti-nuclear antigen reactivity	VRC07-523LS does reacts with a small subset of nuclear antigens
Assessment of anti-phospholipid characteristics by impact on activated partial thromboplastin time (aPTT)	VRC07-523LS does not impact aPTT by binding phospholipids
Assessment of binding to a human epithelial cell line (HEp-2) by Immunohistochemistry	VRC07-523LS has minimal reactivity with HEp-2 cells [3]
Assessment of potential "off target" binding in a GLP tissue cross-reactivity study with normal adult human and rat (Sprague Dawley) tissues	VRC07-523LS staining that was observed in both human and Sprague-Dawley rat tissues included cytoplasm, cytoplasmic granules, perinuclear, and/or apical cytoplasm of endothelium, epithelial cells, spindle cells, mononuclear cells, granulosa lutein cells, and neural cell processes. VRC07-523LS staining that was observed in human tissues only included cytoplasmic elements of hematopoietic cells, cells/processes associated with peripheral nerve, glial cell processes, reticular cells, mesothelial cells, interstitial cells, and adipocytes, and extracellular proteinaceous material in connective tissue of the sclera. VRC07-523LS staining that was observed in rat tissues only included the cytoplasm of rare decidual cells and lens protein. According to ICH S6(R1) and other references [17, 18], monoclonal antibody binding to cytoplasmic sites generally is considered of little to no toxicologic significance. The specific staining of extracellular proteinaceous material in eye (human tissue) and staining for lens protein in eye (rat tissue) further support the rat as a relevant species to assess safety. Additionally, histologic changes were not observed in the GLP repeat dose toxicology study in the cell types with staining observed in the GLP TCR study.

2.4 *IN VIVO* PRECLINICAL PHARMACOLOGY STUDIES

A summary of the *in vivo* pharmacology studies conducted with VRC07-523LS and similar monoclonal antibodies are presented in Table 2. Refer to the IB for more information about these studies.

Table 2: *In Vivo* Preclinical Pharmacology/Proof-of-Concept Studies

Study Purpose	Study Outcome
Determine if VRC07-523LS, an antibody with increased neutralization potency *in vitro*, would confer greater *in vivo* protection compared to VRC01LS when administered as a single dose IV to male rhesus macaques challenged intrarectally with SHIV-BaLP4	7/12 animals were protected after receiving VRC01LS at 0.3 mg/kg IV, 3/4 animals were protected after receiving VRC07-523LS at 0.2 mg/kg IV and 0/4 were protected after receiving VRC07-523LS at 0.05 mg/kg IV. VRC07-523LS showed >5-fold increase in potency compared to VRC01LS, consistent with its ability to better neutralize viruses *in vitro* [3].
Demonstrate SHIV-SF162P3 challenge protection in male and female rhesus macaques administered a single dose of VRC07-523LS at 20 mg/kg IV	6/6 animals were protected after receiving a single dose of VRC07-523LS at 20 mg/kg IV. The average plasma concentration of VRC07-523LS on the day of the challenge (Day 5) was 114.2 µg/mL.
Determine plasma and rectal secretion concentrations in male rhesus macaques administered 10 mg/kg of VRC07-523LS IV	When administered IV at a single dose of 10 mg/kg in rhesus macaques (n=4), the half-life of VRC07-523LS was about 10 days, a 2-fold increase compared to VRC07. Plasma concentrations of VRC07-523LS exceeded 10 µg/mL at day 14 and were greater than 2 µg/mL at day 28 [3]. Detectable concentrations (>10 ng/mL) of VRC07-523LS were measured in rectal secretions for at least 14 days (last collection point) in the 2 animals tested.
Determine plasma, mucosal secretions and tissue concentrations in male and female cynomolgus macaques administered 10 mg/kg of VRC07-523LS IV	When administered IV at a single dose of 10 mg/kg in cynomolgus macaques, the half-life of VRC07-523LS was about 12 days. In all 4 animals, plasma concentrations of VRC07-523LS exceeded 10 µg/mL at day 14 and were greater than 3 µg/mL at day 28. Detectable concentrations of VRC07-523LS were found in rectal and vaginal secretions and tissues for at least 28 days (last collection point).
Determine plasma, rectal, vaginal and nasal secretions concentrations in male and female rhesus macaques administered 10 mg/kg of VRC07-523LS SC	When administered SC at a single dose of 10 mg/kg in rhesus macaques, the half-life of VRC07-523LS was about 14 days. In all 6 animals, detectable concentrations of VRC07-523LS were found in rectal, vaginal and nasal secretions for at least 49 days (last collection point).

3. STUDY OBJECTIVES

3.1 PRIMARY OBJECTIVES

- To evaluate the safety and tolerability of VRC-HIVMAB075-00-AB administered as a single dose at 1 mg/kg IV, 5 mg/kg IV, 20 mg/kg IV, 40 mg/kg IV, and 5 mg/kg SC to healthy adults.
- To evaluate the safety and tolerability of VRC-HIVMAB075-00-AB administered at 20 mg/kg IV by repeat dosing every 12 weeks for a total of 3 infusions to healthy adults.
- To evaluate the safety and tolerability of VRC-HIVMAB075-00-AB administered at 5 mg/kg SC by repeat dosing every 12 weeks for a total of 3 injections to healthy adults.

3.2 SECONDARY OBJECTIVES

- To evaluate the pharmacokinetics of VRC-HIVMAB075-00-AB at each dose level through 24 weeks after the last dose.
- To determine whether anti-drug antibody (ADA) to VRC07-523LS can be detected in recipients of VRC-HIVMAB075-00-AB.

3.3 EXPLORATORY OBJECTIVES

- To determine if measurable levels of VRC-HIVMAB075-00-AB can be found in oral secretions of subjects.
- To evaluate for evidence of functional activity of VRC-HIVMAB075-00-AB in samples collected at representative timepoints throughout the study.
- To test subjects for the IgG1 allotypes in order to evaluate allotype-specific effects on the VRC07-523LS pharmacokinetics.

4. STUDY DESIGN

This is an open-label, dose-escalation study to examine the safety, tolerability, dose, and PK of VRC07-523LS in healthy adults. The hypothesis is that VRC07-523LS administration will be safe by the IV and SC routes. The secondary hypothesis is that VRC07-523LS will be detectable in human sera with a definable half-life. The study schema is shown in Table 3.

Table 3: VRC 605 Study Schema

Group	Subjects	Administration Schedule		
		Day 0	Week 12	Week 24
1	3	1 mg/kg IV		
2	3	5 mg/kg IV		
3	3	5 mg/kg SC		
4	3	20 mg/kg IV		
5	3	40 mg/kg IV		
6	5	5 mg/kg SC	5 mg/kg SC	5 mg/kg SC
7	5	20 mg/kg IV	20 mg/kg IV	20 mg/kg IV
Total*	25	*The expected enrollment is 25 subjects. Enrollment up to a total of 40 subjects is permitted if additional subjects are necessary for safety or PK evaluations (Section 4.3).		

Enrollment will begin in the 1 mg/kg IV dose group (Group 1). Enrollments into the subsequent dose and route groups may proceed after dose and route escalation reviews (Section 4.3). Subjects in Groups 1 through 5 will be expected to be available for follow-up visits during 24 weeks of study participation; subjects in Groups 6 and 7 will be expected to be available for follow-up visits during 48 weeks of study participation

For each new dose level (1 mg/kg, 5 mg/kg, 20 mg/kg and 40 mg/kg) and for the initial SC group, following the first product administration, the study team will wait at least 2 days before administering VRC07-523LS to a second subject within the same group. Safety review decisions and the status of the enrollment process will be transparent to the Protocol Safety Review Team (PSRT) throughout the trial and discussed during the weekly safety review.

Safety laboratory samples will be collected throughout the study as per the Schedule of Evaluations. Subjects will keep a daily diary of solicited systemic symptoms for 3 days after each product administration. PK samples will be collected at specified intervals through 24 weeks after a subject's last product administration.

When the subject agrees, optional oral samples will be collected at specified intervals for the purpose of detecting if measurable levels of VRC07-523LS can be found in oral mucosa.

The study will be conducted by the VRC Clinical Trials Program at the NIH Clinical Center (NIH CC).

4.1 STUDY POPULATION

All inclusion and exclusion criteria must be met for eligibility.

4.1.1 Inclusion Criteria

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

1. Able and willing to complete the informed consent process.
2. 18 to 50 years of age.
3. Based on history and examination, must be in good general health and without history of any of the conditions listed in the exclusion criteria.
4. Willing to have blood samples collected, stored indefinitely, and used for research purposes.
5. Able to provide proof of identity to the satisfaction of the study clinician completing the enrollment process.
6. Willing to adhere to reduced risk sexual behavior during study participation.
7. Screening laboratory values within 84 days prior to enrollment must meet the following criteria:
    - WBC 2,500-12,000/mm3.
    - WBC differential either within institutional normal range or accompanied by the PI or designee approval.
    - Platelets = 125,000 – 400,000/mm3.
    - Hemoglobin within institutional normal range.

- Creatinine ≤ 1.1 x ULN.
- ALT ≤1.25 x ULN.
- Negative for HIV infection by the FDA approved method of detection.

Female-Specific Criteria:

8. If a woman is of reproductive potential and sexually active with a male partner, then she agrees to use an effective means of birth control from the time of study enrollment until the last study visit, or to be monogamous with a partner who has had a vasectomy.
9. 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 volunteer will be excluded if one or more of the following conditions apply:

1. Previous receipt of licensed or investigational monoclonal antibody.
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. Woman who is breast-feeding, or planning to become pregnant during the study participation.
6. Receipt of any investigational study agent within 28 days prior to enrollment.
7. Any other chronic or clinically significant medical condition that in the opinion of the investigator would jeopardize the safety or rights of the volunteer, including but not limited to: diabetes mellitus type I, chronic hepatitis; OR clinically significant forms of: drug or alcohol abuse, asthma, autoimmune disease, psychiatric disorders, heart disease, or cancer.

4.2 Clinical Procedures and Laboratory Assays

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

4.2.1 Screening

Screening for this study will be completed through the Vaccine Research Center's screening protocol, VRC 500 (NIH 11-I-0164). Volunteers will be recruited through Institutional Review Board (IRB)-approved advertising. The evaluations and sample collection that will be included in screening are a medical history, physical exam, any laboratory tests needed to confirm eligibility, and pregnancy test for females of reproductive potential. Additional assessments of health will be conducted at screening based on clinical judgment. Storage samples of PBMCs, plasma and serum will also be collected. Informed consent documents will be reviewed. Counseling related to potential risks of the study product, pregnancy prevention and HIV prevention will be performed. An Assessment of Understanding (AoU) will be completed in association with enrollment into VRC

605. Screening records will be kept to document the reason why an individual was screened but not enrolled.

4.2.2 Enrollment, Study Days and Visit Numbers

In this study, enrollment is defined as the assignment of a study identification number and study group schedule (Section 6.3.1) 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.

Day 0 is defined as the day of first VRC07-523LS administration. Day 0 may occur on the same day as enrollment or up to 6 weeks after. 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 III. Since there may be more than one research sampling timepoint of interest per study day, each sample collection timepoint has its own "Visit Number." For this reason, there may be more than one visit number recorded on the same calendar date.

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

4.2.3 Administration of VRC07-523LS

All study product administrations will be completed according to the assigned group. For women of childbearing potential, product administration may not proceed unless a negative pregnancy test has been obtained within the previous 24 hours. Prior to each product administration, temperature, blood pressure, heart rate (pulse) and weight will be collected and a targeted physical examination (based on signs, reported symptoms or interim medical history) may be conducted. In all study groups, the subject will be observed for at least 4 hours following each product 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. VRC07-523LS will be administered with approximately 100 mL normal saline IV over about 30 minutes or longer. If the subject experiences side effects during the infusion, the rate of infusion may be slowed or stopped to alleviate the symptoms.

If a subject is assigned to a SC administration group, the SC administration site(s) to be used will be discussed with the subject and 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 and syringe SC injection methods with about 2.5 mL per injection site. Up to 4 SC injection sites may be used if deemed necessary by the clinician. SC administration sites should be at least 2 inches apart.

Procedures for VRC07-523LS preparation and administration are described in Section 7.

4.2.4 Solicited Adverse Events and Clinical Follow-up

Subjects will be asked to record temperature and systemic symptoms daily for 3 days after each product administration. Subjects will be trained and encouraged to use the electronic database to record reactogenicity but will have the option to use the paper diary card. When the 3-day diary

card parameters are recorded directly by the subject into the database, the subject's electronic record will be available to clinicians in real time, and will be the source for these data. If concerns arise based on the electronic data, or if a subject uses a paper diary card, clinicians may follow up with additional phone calls during reactogenicity period as needed. The paper diary may be the source document, if used by the subject. When neither a written nor electronic diary is available from the subject, the clinician will note the source of reactogenicity information recorded in the study database.

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

Local symptoms will be assessed and recorded by the clinicians. Local reactogenicity parameters will include pain/tenderness, swelling, redness, bruising, and pruritus (itchiness) at the product administration site. Clinicians will assess the product administration site(s) for local reactogenicity on the day of product administration and during the scheduled follow-up timepoints for all groups.

Events that may require a clinic visit include rash, urticaria, fever of 38.6˚C (Grade 2) or higher lasting greater than 24 hours or significant impairment in the activities of daily living (such as those consistent with Grade 2 or higher impairment). Additionally, arthralgia or other clinical concerns may prompt a study visit based on the judgment of a study clinician.

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

4.2.5 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.

4.2.6 Oral Mucosa Samples

To understand tissue distribution of VRC07-523LS and how long after administration it may be detectable, this protocol includes exploratory collection of oral mucosa samples. Subjects will be offered the option of participating in the oral sampling schedule, but it will not be mandatory. Samples will be collected using small ophthalmic sponges designed for clinical use.

Oral swabs for research may be collected per the Schedule of Evaluations, Appendix III.

4.2.7 Schedule of Evaluations

The Schedule of Evaluations, Appendix III, provides details on the study schedule and the permitted visit windows. Schedule 1 is for the IV dose escalation groups receiving one injection (Groups 1, 2, 4, and 5), Schedule 2 is for the SC dose group receiving one injection (Group 3). Schedule 3 and Schedule 4 are for the groups receiving repeat dosing; Group 6 (5 mg/kg SC) and Group 7 (20 mg/kg IV). The schedules also include instructions for evaluations of subjects who discontinue

product administration. After enrollment, deviations from the visit windows are discouraged but will be permitted at the discretion of the PI or designee and will be recorded as protocol deviations.

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

Any evaluation for an AE or possible exacerbation of a pre-existing condition may be evaluated at study team discretion as a "protocol related" evaluation.

4.2.8 Concomitant Medications

Only routine prescription medications will be entered in the database at the time of enrollment. Subsequently, concomitant medications associated with an AE that requires expedited reporting or the development of a new chronic condition requiring ongoing medical management will be recorded in the database. Receipt of a FDA-approved vaccine at any time during the study will be recorded in the database (clinicians should work with subjects regarding the timing of licensed vaccines relative to study product administration). Otherwise, concomitant medications taken throughout the study will be recorded in the subject's chart as needed for general medical documentation but will not be recorded in the database.

4.3 CRITERIA FOR DOSE AND ROUTE ESCALATION

There are three dose escalation reviews in this study and one route escalation review. The Protocol Safety Review Team (PSRT, Section 8.9) will conduct an interim safety data review before dose escalation and repeat dosing may occur. The PSRT must assess the data as showing no significant safety concerns before proceeding with enrollment of the next groups.

- The first dose escalation review (from 1 mg/kg IV to 5 mg/kg IV) will occur when at least 3 subjects who received the 1 mg/kg IV dose have completed 2 weeks of safety follow-up visits. The PSRT review will determine if enrollments in Group 2 may begin.
- The only route escalation review and the second dose escalation review (from 5 mg/kg IV to 5 mg/kg SC and 20 mg/kg IV, respectively) will occur when at least 3 subjects who received the 5 mg/kg IV dose have completed 2 weeks of safety follow-up visits. The PSRT review will determine if enrollments in Group 3 (5 mg/kg SC), Group 6 (5 mg/kg SC by repeat dosing), Group 4 (20 mg/kg IV) and Group 7 (20 mg/kg IV by repeat dosing) may begin.
- The third dose escalation review (from 20 mg/kg IV to 40 mg/kg IV) will occur when at least 3 subjects who received the 20 mg/kg IV dose have completed 2 weeks of safety follow-up visits. This review will determine if enrollments in Group 5 (40 mg/kg IV) may begin.
- Additionally, the second and third doses can be administered in Groups 6 and 7 once the initial dose is assessed as safe for further evaluation.

If the first product administration is not completed or there are discontinuations from the study before there are sufficient data to conduct the dose escalation review for a group, then extra subjects may be enrolled into that group in order to have the requisite data on at least 3 subjects. 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 at a given dose group.

The IRB will be provided with documentation of the safety review process and notification of the dose escalation. Consultation with the IRB and FDA, if needed, as per study pause criteria (Section 4.5) will occur if indicated by the review. One outcome of a dose escalation review may be to recommend evaluation of additional subjects at the current dose and reassess for safety before proceeding to a higher dose.

4.4 CRITERIA FOR DISCONTINUATION OF VRC07-523LS ADMINISTRATION

Under certain circumstances, a subject may be terminated from participating in study product administrations. Subjects who receive at least one VRC07-523LS administration will continue follow-up according to the protocol Schedule of Evaluations, except that the research sample collections will be discontinued for pregnant women or others in which it is contraindicated. The study team will notify the antiretroviral pregnancy registry (http://www.apregistry.com) of any pregnancies that occur after receiving VRC07-523LS for any subject still on study. Specific events that will require discontinuing a subject from receiving the study product include:

1. Pregnancy;
2. Grade 3 AE assessed as related to the study product (with the exception that self-limited Grade 3 solicited reactogenicity does not require discontinuation of product administration);
3. Grade 4 AE assessed as related to the study product;
4. Immediate hypersensitivity reaction associated with the study product;
5. Intercurrent illness that is not expected to resolve prior to the next scheduled study product administration which is assessed by the PI (or designee) to require withdrawal from the product administration;
6. Repeated failure to comply with protocol requirements;
7. Co-enrollment into a study in which other investigational research agents will be administered before the subject has completed the follow-up after the last VRC07-523LS administration;
8. The IND sponsor or the study PI decide to stop or cancel the study;
9. The IRB, Office for Human Research Protections (OHRP) or the FDA halt the study.

4.5 CRITERIA FOR PAUSING THE STUDY AND RESUMING THE STUDY

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

One (or more) subject experiences a **Serious Adverse Event** (SAE) that is assessed as related to study product, or

Two (or more) subjects experience the same **Grade 3 or higher AEs** assessed as related to study product (other than self-limited Grade 3 solicited reactogenicity AEs).

Plan for Review of Pauses and Resuming Rules:

Study product administration and enrollments would resume only if review of the AEs that caused the pause results in a recommendation to permit further study product administrations and study enrollments. The reviews to make this decision will occur as follows:

Pauses for related SAEs: The IND Sponsor, with participation by the PI, will consult with the FDA to conduct the review and make the decision to resume, amend or close the study and will notify the IRB accordingly.

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

5. SAFETY AND ADVERSE EVENT REPORTING

5.1 ADVERSE EVENTS

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

Severity of AEs will be assessed using the Version 2.0 of the *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events* [November 2014]. The table is available at: http://rsc.tech-res.com/Document/safetyandpharmacovigilance/DAIDS_AE_GRADING_TABLE_v2_NOV2014.pdf. Additional information can be found in Appendix IV.

Reporting of all AEs will occur during the period from first study product administration through 56 days after each study product administration. After this through completion of study participation only serious adverse events (SAEs) and new chronic medical conditions that require ongoing medical management will be recorded as AEs in the study database.

5.2 SERIOUS ADVERSE EVENTS

The term "Serious Adverse Event" (SAE) is defined in 21 CFR 312.32 as follows: "An adverse event or suspected adverse reaction is considered serious if, in the view of either the investigator or the sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse."

"Life-threatening" refers to an AE that at occurrence represents an immediate risk of death to a

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

5.3 ADVERSE EVENT REPORTING TO THE IND SPONSOR

AEs that meet Serious Adverse Event (SAE) Reporting Requirements must be reported and submitted by the clinical site on an expedited basis to the IND Sponsor, VRC/NIAID/NIH, according to Sponsor guidelines as follows:

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

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

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

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

5.3.1 IND Sponsor Reporting to the FDA

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

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

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

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

5.4 REPORTING TO THE INSTITUTIONAL REVIEW BOARD

5.4.1 Unanticipated Problem (UP) Definition

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

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

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

5.4.2 Protocol Deviation Definition

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

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

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

5.4.3 Non-Compliance Definition

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

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

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

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

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

5.4.4 Expedited Reporting to the NIAID IRB

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

- Serious and non-serious UP

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

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

5.4.5 Annual Reporting to the NIAID IRB

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

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

6. STATISTICAL CONSIDERATIONS

6.1 OVERVIEW

This is a Phase I dose-escalation study of the safety and pharmacokinetics of VRC-HIVMAB075-00-AB (VRC07-523LS), a human monoclonal antibody with broad HIV-1 neutralizing activity, administered to healthy adults.

6.2 OBJECTIVES

The primary objective is to evaluate the safety and tolerability of VRC07-523LS administered at 1 mg/kg IV, 5 mg/kg IV, 5 mg/kg SC, 20 mg/kg IV and 40 mg/kg IV as a single dose, and administered at 20 mg/kg IV and 5 mg/kg SC by repeat dosing every 12 weeks for a total of 3 product administrations to healthy adults. Secondary objectives include evaluation of the PKs at each dose level through 24 weeks after the last dose and testing for the presence of ADA against VRC07-523LS. Exploratory objectives include determining if measurable levels of VRC07-523LS can be found in oral secretions, evaluation for evidence of functional activity of VRC07-523LS in collected samples, and evaluation of allotype-specific effects on the VRC07-523LS pharmacokinetics.

6.3 SIZE AND ACCRUAL

Recruitment will target about 25 healthy adults of age 18-50 with 3 subjects in each dose escalation group (Groups 1-5), and 5 subjects in each repeat dosing group (Groups 6 and 7). The permitted accrual is 40 subjects 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.

6.3.1 Treatment Assignments

In this dose-escalation study, subjects will be assigned to the dose group that is open to accrual at the time of enrollment.

When a subject is enrolled into a group but does not begin product administrations, a new eligible subject may be enrolled into the same group. If any replacement is needed in case of subject withdrawal, the replacement subject will be assigned to the same treatment as the dropout subject in order to complete the safety dataset as planned.

Dose escalation rules are described in Section 4.3.

6.3.2 Sample Size Considerations

This study is primarily descriptive. For safety analysis, the goal is to identify safety concerns associated with different VRC07-523LS doses. There may be as few as 3 to 5 subjects in a group at the time of a dose escalation; therefore, this section considers group sizes of both n=3 and n=5.

The ability to identify serious adverse experiences is best expressed by the maximum true rate of SAE that would unlikely be observed and the minimum true SAE rate that would very likely be observed. Within a group of size n=3, there is a 90% chance of observing at least 1 event if the true rate is no less than 0.536 and a 90% chance of observing no event if the true rate is no bigger than 0.034. Within a group of size n=5, there is a 90% chance of observing at least 1 event if the true rate is no less than 0.37 and a 90% chance of observing no event if the true rate is no bigger than 0.02.

Probabilities of observing 0 or more than 1 event are presented in Table 4 for a range of possible true event rates. These calculations provide a complete picture of the sensitivity of this study design to identify potential safety problems with the study product. For example, within the group of size n=3, if the true event rate is 0.01, then there is a probability of 0.97 to observe no event and a probability of <0.001 to observe more than 1 event; while, within the group of size n=5, if the true event rate is 0.01, then there is a probability of 0.951 to observe no event and a probability of 0.001 to observe more than 1 event.

Table 4: Probability of Event for Different Scenarios

True event rate	Within a group (n=3)		Within a group (n=5)	
	Pr(0 event observed)	Pr(more than 1 event observed)	Pr(0 event observed)	Pr(more than 1 event observed)
0.01	0.97	0	0.951	0.001
0.03	0.913	0.003	0.859	0.008
0.05	0.857	0.007	0.774	0.023
0.1	0.729	0.028	0.59	0.081
0.2	0.512	0.104	0.328	0.263
0.3	0.343	0.216	0.168	0.472
0.4	0.216	0.352	0.078	0.663

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

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

Within a group (n=3) 95% confidence interval			Within a group (n=5) 95% confidence interval		
Observed rate	Lower bound	Upper bound	Observed rate	Lower bound	Upper Bound
0/3	0	0.708	0/5	0	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	3/5	0.147	0.947
			4/5	0.284	0.995
			5/5	0.478	1

Tables 4 and 5 apply to the secondary and exploratory endpoints as well.

6.4 STATISTICAL ANALYSIS

6.4.1 Analysis Variables

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

6.4.2 Baseline Demographics

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

6.4.3 Safety Analysis

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

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

Unsolicited AEs: Unsolicited AEs are coded into MedDRA preferred terms. The number and percentages of participants experiencing each specific AE will be tabulated by severity and relationship to treatment. For the calculations in these tables, each participant's adverse experience will be counted once under the maximum severity or strongest recorded causal relationship to treatment.

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

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

6.4.4 Tolerability Evaluation

The tolerability of the medical product represents the degree to which overt adverse effects can be tolerated by the subject [19]. VRC 605 is the first trial of VRC07-523LS in healthy adults. The tolerability evaluation will be mostly descriptive by nature and consist of solicited AEs that occur during the 3 days following each VRC07-523LS administration and reasons for any withdrawal or discontinuation based upon subject discomfort. This early assessment of tolerability of VRC07-523LS will inform which parameters should be solicited or routinely assessed to further characterize the tolerability profile in a larger number of subjects.

6.4.5 Pharmacokinetics Analysis

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

Individual Subject Pharmacokinetic Analysis: A non-compartmental PK analysis will be performed using Phoenix (Centara) or a similar program on the VRC07-523LS concentration data generated from each subject. Calculated PK parameters for IV Groups 1, 2, 4, 5, and 7 will include: area-under-the-curve (AUC), maximum concentration (Cmax), time to Cmax (Tmax), clearance (CL), volume of distribution (Vdz), terminal elimination rate constant (λz) and the terminal half-life ($T_{1/2}$). For Groups 3 and 6, the PK parameters will include AUC, Cmax, Tmax, apparent clearance (CL/F), apparent volume of distribution (Vdz/F), λz and $T_{1/2}$. Cmax and Tmax will be taken directly from the observed concentration-time data. The terminal slope, λz, will be determined from the log-linear portion of the curve and the $T_{1/2}$ calculated as $0.693/\lambda z$. $AUC_{0\text{-}Clast}$ will be determined using the linear trapezoidal method, where C_{last} is the concentration at 12 weeks after the first two doses in Groups 6 and 7 and the concentration at 24 weeks after dose in Groups 1, 2, 4 and 5 and final dose in Groups 6 and 7. If the final sample (C_{last}) has measurable VRC07-523LS concentrations, the remaining AUC after the final concentration ($AUC_{Clast\text{-}inf}$) will be estimated as $Clast/\lambda z$. Data will be summarized based by each dose group and overall for IV administration

groups for CL, Vd and $T_{1/2}$. For Groups 6 and 7, potential accumulation will be assessed as the ratios of the $AUC_{0\text{-}inf}$ and C_{max} for the first and the last doses. The potential for non-linearity PKs among IV groups will be determined by comparing the dose-adjusted ratios for Cmax and AUC between IV groups. Additional compartmental analysis will be performed as warranted by the data.

Population Pharmacokinetic Analyses: Population PK analyses will be performed on the VRC07-523LS PK data following IV and SQ administration to determine compartmental PK parameters with the program NONMEM. One and two compartment PK models will be assessed. Based on prior PK studies of antibodies, including VRC01, 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 not include an exploratory covariate analysis to assess clinical factors as fixed effects associated with VRC07-523LS PK parameters with the exception of dose (5 vs 20 vs 40 mg/kg), and first vs subsequent doses as a fixed effects on CL, Vd_1, and Vd_2. The terminal half-life, $t_{1/2\beta}$ will be determined from CL. Vd_1, Vd_2 and Q. Final model selection will be based on changes in the objective function and graphically by goodness of fit plots. The final population model will be assessed using bootstrap analysis and dose normalized visual posterior predictive check. VRC07-523LS dosing strategies and their ability to achieve and maintain target VRC07-523LS concentrations will be performed using the final population PK model and Monte Carlo simulations with at least 5000 replicates.

6.4.6 Interim Analyses

Preliminary analyses of PKs may be done once per dose level as the data for each dose level is obtained. This will be used to inform decisions about the dose levels to be administered in studies that may begin while VRC 605 is still in progress.

7. PHARMACY PROCEDURES

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

7.1 STUDY PRODUCT AND ADMINISTRATION REGIMEN

VRC-HIVMAB075-00-AB (VRC07-523LS) is supplied at a concentration of 100 mg/mL ± 10 mg/mL in an isotonic, sterile solution; two fill volumes are available: 2.5 ± 0.1 mL in a 3 mL glass vial and 6.25 ± 0.1 mL in a 10 mL glass vial. Vials contain a clear, colorless to yellow liquid essentially free of visible particles; some opaque or translucent particles may be present. The formulation buffer is composed of 50 mM Histidine, 50 mM Sodium Chloride, 5% Sucrose, and 2.5% Sorbitol at pH 6.8. Vials are intended for single-use only and thus do not contain a preservative.

In this trial, dose is limited or established based on subject weight. In calculating the dose to administer and number of vials to thaw, it should be assumed that the concentration is 100 mg/mL and that a volume of at least 6 mL can be withdrawn from a vial. Preparation of VRC07-523LS for IV administration will require a 100 mL bag of 0.9% sodium chloride, USP (normal saline). Note that the normal saline bags referred to as "100 mL bags" in the IV administration instructions will typically have 103 mL volume before any VRC07-523LS is added and this is acceptable in the context of the instructions below. Preparation of VRC07-523LS for SC administration will not require any diluent.

There are 7 different schedules in the study described in Section 4.

7.2 VRC HIVMAB075-00-AB (VRC07-523LS) VIALED PRODUCT

The VRC07-523LS product label designates the long-term storage temperature as -35°C to -15°C. Clinical site storage in a qualified, continuously monitored, temperature-controlled freezer with temperature excursions -45°C to -10°C is acceptable.

Following thaw, VRC07-523LS vials may be stored for up to 24 hours at controlled room temperature (maximum 27°C) and/or up to 2 weeks at 2ºC to 8ºC. Product may not be stored in direct sunlight. If stored at 2-8°C, vials must be equilibrated at controlled room temperature (maximum 27ºC) for a minimum of 30 minutes and may be held at room temperature for up to 8 hours prior to product preparation.

7.3 TEMPERATURE EXCURSIONS

The site pharmacist must promptly report any storage temperature excursions outside of the normal allowance for the storage device to the IND Sponsor (Appendix II). The affected product must be quarantined in a separate area. The IND Sponsor will notify the site pharmacist if continued clinical use of the product is acceptable.

7.4 PREPARATION OF STUDY PRODUCT FOR ADMINISTRATION

This section describes how the site pharmacist will prepare the study product for administration and how the clinician will administer the product. Clinician instructions on how to select an administration site are in Section 4.2.3.

VRC07-523LS is a highly concentrated protein solution and may develop white, opaque to translucent particles after thawing. When particles are observed, they may disappear after a few hours at room temperature or storage at 2ºC to 8ºC.

The following instructions apply to thawing VRC07-523LS:

1. Thaw vial(s) for a minimum of 1 hour at controlled room temperature (maximum 27°C) after removing from the freezer.
2. Keep the material at room temperature during the entire preparation period until use, up to the maximum storage times described in Section 7.2.
3. Prior to preparation for administration, vials should be swirled for 30 seconds with sufficient force to resuspend any visible particles, yet avoiding foaming. DO NOT SHAKE THE VIALS. If particles are observed, return the vials to 2°C to 8°C storage. If the particles redissolve within the maximum storage times described in Section 7.2, the vials may be used for product preparation. **If particles continue to be observed, do not use the vialed product for SC or IV administration**. Refrigerated product must be equilibrated at controlled room temperature (maximum 27ºC) for a minimum of 30 minutes before preparation and must be used within 8 hours of any subsequent return to room temperature.
4. If the thawed material is not administered within 24 hours of thaw, follow the storage information provided in Section 7.2.

Preparation is to be done using aseptic technique, in a laminar flow biosafety cabinet. Assure that only the required vials are present in the preparation unit during dilution, and medication labels are strictly segregated to avoid mix-ups. More information on product preparation can be found in the IB.

7.4.1 VRC-HIVMAB075-00-AB: Preparation for Administration Intravenously

For each IV infusion order, the subject's weight and dose level or randomization code will be included in the pharmacy order. To prepare an IV infusion, the pharmacist will calculate the total milligrams needed, retrieve the minimum number of thawed, particle free vials needed to prepare the full dose and add the calculated total mg needed to a 100 mL bag of normal saline using good pharmacy practices to maintain sterility. Prior to preparation for administration, vials should be gently swirled for 30 seconds avoiding foaming. DO NOT SHAKE THE VIAL. Typically, 50 to 100 of additional volume may be added to a 100 mL bag of normal saline. Each pharmacist should test the capacity of the brand of saline bags that will be used at the site to confirm the capacity to add additional volume.

An in-line filter infusion set must be used for IV product administrations. In-line filters must comply with the following specifications: 1.2 micron PES (polyethersulfone) filter membrane, DEHP-free, latex-free (equivalent to Braun #473994 filter extension set). When the in-line filter is added to the tubing, prime the administration set. Flush the administration set with about 30 mL or appropriate volume of normal saline at the end of product administration

The study product solution will typically be administered IV over about 15 to 30 minutes or more as needed using a volumetric pump. The total time needed to administer the dose may be longer based on factors such as subject tolerance. The rate of infusion may range from 10-20 mg/kg/hr with the lowest dose group to 80-160 mg/kg/hr with the highest dose group. The mL/hr infusion rate may vary based on the total volume needed to administer a full dose.

7.4.2 VRC-HIVMAB075-00-AB: Preparation for Administration Subcutaneously

For each SC administration order, the subject's weight and dose level or randomization code will be included in the pharmacy order. To prepare a SC administration dose, the pharmacist will calculate the total mg needed and retrieve the minimum number of thawed, particle free vials needed to prepare the full dose. Prior to preparation for administration, vials should be gently swirled for 30 seconds avoiding foaming. DO NOT SHAKE THE VIALS. If particles are observed, follow instructions in Section 7.4.

The needed volume of VRC07-523LS must be withdrawn from the vial into 1 to 4 syringes (BD Luer-Lok mL syringe; REF # 309657) using a 5 micron filter needle (BD Blunt Fill Needle – Filter , 18G 1 ½ inch; REF# 305211). A new filter needle must be used for each syringe. The filter needle must be discarded prior to dispensing and replaced with a needle suitable for SC injection at the time of administration.

The product may be administered by direct SC injection with needle and syringe or using a SC infusion pump at a rate of 15 mL/hr. The clinician will use proper SC technique to ensure administration into SC fatty layer and a slow push to minimize discomfort or the excessive distention of overlying skin. The length of time to complete the infusion will vary depending on the subject's weight and tolerance of the infusion rate.

7.4.3 VRC -HIVMAB075-00-AB (VRC07-523LS) Prepared Product (IV Bag and Syringe)

After product preparation in IV bags, the prepared VRC07-523LS may be stored at 2oC to 8oC up to 24 hours or at room temperature (maximum 30oC) for a maximum of 8 hours total including the infusion time. Product may not be stored in direct sunlight. If stored at 2oC to 8oC, prepared product must be equilibrated at room temperature (maximum 30oC) for a minimum of 30 minutes prior to product administration.
After preparation in syringes for SC administration, the prepared VRC07-523LS may be stored at 2oC to 8oC up to 24 hours or at room temperature (maximum 30oC) up to 4 hours. Product may not be stored in direct sunlight.

Each institution will need to follow their policies for expiration dates if shorter than the timeframes specified here or in the IB.

7.5 RISKS

Risks of Administration of MAbs: Administration of MAbs may have a risk of immune reactions such as acute anaphylaxis, serum sickness and the generation of antibodies. However, these reactions are rare and more often associated with MAbs targeted to human proteins or with the use of murine MAbs that would have a risk of human anti-mouse antibodies [20]. In this regard, because VRC07-523LS is targeted to a viral antigen and is a human MAb, it is expected to have a low risk of such side effects.

Typically, the side effects of MAbs are mild and may include reactions at 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 [20]; however, this is not expected to be a risk for a MAb targeted to a viral antigen.

It is known from published experience with human MAbs directed against the cell surface targets on lymphocytes that infusion of a MAb may be associated with cytokine release, causing a reaction known as “cytokine release syndrome” (CRS) [21]. Most infusion-related events occur within the first 24 hours after beginning administration. Severe reactions, such as anaphylaxis, angioedema, bronchospasm, hypotension and hypoxia, are infrequent and more often associated with MAbs targeted to human proteins or with non-human MAb, such as a murine MAb [20]. CRS reactions most commonly occur within the first few hours of beginning infusion and with the first MAb infusion received. This is because the cytokine release is associated with lysis of the cells targeted by the MAb and the burden of target cells is greatest at the time of the first MAb treatment. With licensed therapeutic MAbs, CRS is managed by temporarily stopping the infusion, administering histamine blockers and restarting the infusion at a slower rate [22].

Delayed allergic reactions to a MAb may include a serum sickness type of reaction, which is characterized by urticaria, fever, lymph node enlargement, and joint pains. Symptoms may not appear until several days after the exposure to the Mab. This type of reaction is noted to be more common with chimeric types of MAb [20].

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 future MAb studies.

Risks of Blood Drawing: Blood drawing may cause pain and bruising and, infrequently, may cause a feeling of lightheadedness or fainting. Rarely, it may cause infection at the site where blood is taken. In this study, an IV line that can be used for blood collection may be placed and 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 Oral Mucosa Sample Collection: Collection of samples by swabs and wicks rubbed over the mucosal surfaces may cause momentary discomfort and, in some cases, minor bleeding.

7.6 BENEFITS

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

7.7 INSTITUTIONAL REVIEW BOARD

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

The investigator must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent document. The investigator will notify the IRB of unanticipated problems, non-compliance, deviations from the protocol, and 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.

7.8 SUBJECT CONFIDENTIALITY

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

7.9 PLAN FOR USE AND STORAGE OF BIOLOGICAL SAMPLES

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

7.9.1 Use of Samples, Specimens and Data

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

7.9.2 Storage and Tracking of Blood Samples and Other Specimens

All of the stored study research samples are labeled by a code that only the VRC Clinic can link to the subject. Samples are stored at the NIAID Vaccine Immune T-Cell and Antibody Laboratory (NVITAL), 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).

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

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

At the time of protocol termination, samples will remain in the NVITAL facility or VRC laboratories or, after IRB approval, transferred to another repository. Regulatory oversight of the stored samples and data may be transferred to a stored samples protocol as part of the IRB-approved termination plan. Data will be archived by the VRC in compliance with requirements for retention of research records, or after IRB and study sponsor approval, it may be either destroyed or transferred to another repository.

7.9.4 Loss or Destruction of Samples, Specimens or Data

The NIH Intramural Protocol Deviation definition related to loss of or destruction of samples or data will be followed. 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.

7.10 SUBJECT IDENTIFICATION AND ENROLLMENT

All study activities will be carried out at the NIH CC. Study subjects will be recruited through on-site and off-site advertising done for the screening protocol, VRC 500 (NCT 01375530) (https://clinicaltrials.gov/ct2/show/NCT01375530?term=VRC+500&rank=1). Effort will be made to include women and minorities in proportions similar to that of the community from which they are recruited and will be limited to persons at least 18 years of age and no older than 50 years of age at enrollment.

7.10.1 Participation of Children

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

7.10.2 Participation of NIH Employees

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

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

7.11 COMPENSATION

Subjects will be compensated for time and inconvenience in accordance with the standards for compensation of the Clinical Research Volunteer Program. Study product administration accompanied by the same day PK blood draws combined will be $375; product administration visits without PK blood draws will be $325. The compensation will be $175 for scheduled visits that include oral swabs and blood drawing, $75 for clinic visits that do not include a blood draw or procedure, and $25 for completion of each electronic diary.

7.12 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.

8. ADMINISTRATIVE AND LEGAL OBLIGATIONS

8.1 PROTOCOL AMENDMENTS AND STUDY TERMINATION

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

The IND Sponsor, NIAID IRB, 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.

8.2 STUDY DOCUMENTATION AND STORAGE

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

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

8.3 STUDY MONITORING, DATA COLLECTION AND DATA SHARING

8.3.1 Protocol Monitoring Plan

The IND Sponsor or their authorized representatives are responsible for ensuring integrity of study data and compliance with the protocol. The PI will allow the study monitors, the IRB and the FDA to inspect study documents (e.g., consent forms, drug distribution forms, and case report forms) and pertinent hospital or clinic records for confirmation of the study data. Site visits by study monitors will be made to monitor the following: study operations, quality of data collected in the research records, the accuracy and timeliness of data entered in the database, and to determine that all process and regulatory requirements are met. Study monitoring visits will occur as defined by the IND Sponsor approved monitoring plan.

8.3.2 Data Collection

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

8.3.3 Source Documents

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

8.3.4 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.

8.4 LANGUAGE

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

8.5 POLICY REGARDING RESEARCH-RELATED INJURIES

The NIH CC will provide short-term medical care for any injury resulting from participation in this research. In general, the 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.

9. REFERENCES

1. UNAIDS, *Fact sheet: 2015 statistics.* 2015.

2. Wu, X., Z.Y. Yang, Y. Li, C.M. Hogerkorp, W.R. Schief, et al., *Rational design of envelope identifies broadly neutralizing human monoclonal antibodies to HIV-1.* Science, 2010. **329**(5993): p. 856-61.

3. Rudicell, R.S., Y.D. Kwon, S.Y. Ko, A. Pegu, M.K. Louder, et al., *Enhanced Potency of a Broadly Neutralizing HIV-1 Antibody In Vitro Improves Protection against Lentiviral Infection In Vivo.* J Virol, 2014. **88**(21): p. 12669-82.

4. Kwon, Y., I. Georgiev, S. O'Dell, W. Shi, G. Chuang, et al., *Structure-guided modification and optimization of antibody VRC07.* Retrovirology, 2012. **9**(Suppl 2): p. O34.

5. Wu, X., C. Wang, S. O'Dell, Y. Li, B.F. Keele, et al., *Selection pressure on HIV-1 envelope by broadly neutralizing antibodies to the conserved CD4-binding site.* J Virol, 2012. **86**(10): p. 5844-56.

6. Ko, S.-Y., A. Pegu, R.S. Rudicell, Z.-y. Yang, M.G. Joyce, et al., *Enhanced neonatal Fc receptor function improves protection against primate SHIV infection.* Nature, 2014. **advance online publication**.

7. Zalevsky, J., A.K. Chamberlain, H.M. Horton, S. Karki, I.W. Leung, et al., *Enhanced antibody half-life improves in vivo activity.* Nat Biotechnol, 2010. **28**(2): p. 157-9.

8. Montefeori, D.C., *Measuring HIV Neutralization in a Luciferase Reporter Gene Assay*, in *HIV Protocols, Second Edition, Vol. 485*, V.R. Prasad, and Kalpana, G.V., Editor. 2009, Humana Press: New York, NY. p. 395-405.

9. Ozaki, D.A., H. Gao, C.A. Todd, K.M. Greene, D.C. Montefiori, et al., *International technology transfer of a GCLP-compliant HIV-1 neutralizing antibody assay for human clinical trials.* PLoS One, 2012. **7**(1): p. e30963.

10. Todd, C.A., K.M. Greene, X. Yu, D.A. Ozaki, H. Gao, et al., *Development and implementation of an international proficiency testing program for a neutralizing antibody assay for HIV-1 in TZM-bl cells.* J Immunol Methods, 2012. **375**(1-2): p. 57-67.

11. Allen, J.C. and H.G. Kunkel, *Antibodies to genetic types of gamma globulin after multiple transfusions.* Science, 1963. **139**(3553): p. 418-9.

12. Jefferis, R. and M.P. Lefranc, *Human immunoglobulin allotypes: possible implications for immunogenicity.* MAbs, 2009. **1**(4): p. 332-8.

13. Kickler, T.S., P.M. Ness, H.G. Braine, L. Richardson, and M. Farkosh, *The expression of IgG allotypes on platelets and immunization to IgG allotypes in multitransfused thrombocytopenic patients.* Blood, 1990. **76**(4): p. 849-52.

14. Lynch, R.M., E. Boritz, E.E. Coates, A. DeZure, P. Madden, et al., *Virologic effects of broadly neutralizing antibody VRC01 administration during chronic HIV-1 infection.* Sci Transl Med, 2015. **7**(319): p. 319ra206.

15. Ledgerwood, J.E., E.E. Coates, G. Yamshchikov, J.G. Saunders, L. Holman, et al., *Safety, pharmacokinetics and neutralization of the broadly neutralizing HIV-1 human monoclonal antibody VRC01 in healthy adults.* Clin Exp Immunol, 2015.

16. DHHS. *Panel On Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf. Assessed February 16, 2016*.

17. Hall, W.C., S.A. Price-Schiavi, J. Wicks, and J.L. Rojko, *Tissue Cross-Reactivity Studies for Monoclonal Antibodies: Predictive Value and Use for Selection of Relevant Animal Species for Toxicity Testing*, in *Preclinical Safety Evaluation of Biopharmaceuticals: A Science-Based Approach to Facilitating Clinical Trials (ed J. A. Cavagnaro)*. 2008, John Wiley & Sons, Inc.: Hoboken, NJ, USA. p. 208-40.

18. Leach, M.W., W.G. Halpern, C.W. Johnson, J.L. Rojko, T.K. MacLachlan, et al., *Use of tissue cross-reactivity studies in the development of antibody-based biopharmaceuticals: history, experience, methodology, and future directions.* Toxicol Pathol, 2010. **38**(7): p. 1138-66.

19. FDA, *Guidance for Industry: E9 Statistical Principles for Clinical Trials*. 1998, U. S. DHHS, FDA, CDER, CBER.

20. Hansel, T.T., H. Kropshofer, T. Singer, J.A. Mitchell, and A.J. George, *The safety and side effects of monoclonal antibodies.* Nature reviews. Drug discovery, 2010. **9**(4): p. 325-38.

21. Bugelski, P.J., R. Achuthanandam, R.J. Capocasale, G. Treacy, and E. Bouman-Thio, *Monoclonal antibody-induced cytokine-release syndrome.* Expert review of clinical immunology, 2009. **5**(5): p. 499-521.

22. Vogel, W.H., *Infusion reactions: diagnosis, assessment, and management.* Clin J Oncol Nurs, 2010. **14**(2): p. E10-21.

Appendix I: Study Informed Consent Form

Text to be included in the NIH Clinical Center Informed Consent Template

TITLE: VRC 605: A Phase 1 Dose-Escalation Study of the Safety and Pharmacokinetics of a Human Monoclonal Antibody, VRC-HIVMAB075-00-AB (VRC07-523LS), Administered Intravenously or Subcutaneously to Healthy Adults

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH). First, we want you to know that:

Taking part in NIH research is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

PURPOSE AND PLAN OF THE STUDY

This is the study of an experimental product called "VRC07-523LS." The U.S. Food and Drug Administration (FDA) allows it to be used for research only. VRC07-523LS is an antibody directed against HIV virus. The human body uses antibodies as one way to help fight infection. There is currently no cure for HIV or vaccine to prevent it.

The main purpose of this study is to see if the experimental product is safe and well-tolerated. We will study the amount of VRC07-523LS in the body and how it changes over time. We will check to see if people who get VRC07-523LS make an immune response (antibody) to it.

About 25 to 40 people will participate in this study at the NIH Clinical Center in Bethesda, Maryland. The study will have about 13-27 clinic visits over 24-48 weeks for each person, depending on the study group.

STUDY PRODUCT

VRC07-523LS is a monoclonal antibody or "MAb." An antibody is a protein that is used by the immune system to find and block bacteria and viruses, like HIV. Monoclonal means that all the antibodies in the product are the same. The formal name for the product is VRC-HIVMAB075-00-AB.

VRC07-523LS is a human antibody but it is a genetically modified synthetic product. It was made based on an antibody that was first found in an HIV-infected person. Although the antibody was found in a human, the product is not made by collecting it from a human. VRC07-523LS was developed by the Vaccine Research Center (VRC) at NIH. This product was made in

a drug manufacturing laboratory. This is the first study to give VRC07-523LS to humans.

VRC07-523LS is similar to the monoclonal antibody VRC01 and was manufactured in a similar way. VRC01 has been given to over 150 healthy and HIV-infected adults and has been found to be safe and well-tolerated.

VRC07-523LS will not protect you from HIV infection. Because we have never tested this product in humans, we assume that it cannot protect against HIV infection. You cannot get HIV from VRC07-523LS because there are no parts of HIV in it.

In laboratory and animal studies, VRC07-523LS was shown to attach to and inactivate many types of HIV viruses. We do not know if the product will act the same way when given to humans. It will take many studies to learn if the product will be useful for preventing or treating HIV. This study alone will not answer this question.

ELIGIBILITY

You are eligible to participate in this study because you have completed the screening process and are known to be the following:

- 18 to 50 years old
- In general good health without significant medical problems as determined at screening
- Willing to get VRC07-523LS
- Willing to donate blood samples for future research
- Willing to be tested for HIV infection
- If female and able to get pregnant: willing to use birth control for the whole study.

STUDY PROCEDURES

The study will have 7 groups. Each group will have about 3-5 people in it. The groups are defined by the dose of VRC07-523LS and how it is given. Most people will get VRC07-523LS by the intravenous (IV) route, meaning into a vein. Some people will get VRC07-523LS by the subcutaneous (SC) route, meaning into the fatty tissue under the skin. Both methods use a needle. The product administration visit(s) will last about 8 hours. Other clinic visits will take about 2 hours.

The study will last about 24 weeks for people in Groups 1-5 because they will only get the study product one time. The study will last for about 48 weeks for people in Groups 6 and 7 because they will get the study product three times.

People in Groups 1-5 will get different doses of the study product 1 time so we can see how long it lasts in the body and if higher doses are safe.

People in Groups 6 and 7 will get the study product 3 times instead of 1 time so we can see if repeat doses are better. We also want to see if it is better to give the study product by the IV or SC routes. This information will be helpful for future uses of the product.

If you agree to take part in this study, you will get 1 or 3 doses of VRC07-523LS, depending on the group. You will know how many doses you will get once you enroll. The amount of study product you will get is calculated based on your body weight. We will measure your weight on the day the study product is given to calculate the dose.

The Study Groups are shown in the following table:

Group	Subjects	Schedule		
		Day 0	Week 12	Week 24
1	3	1 mg/kg IV		
2	3	5 mg/kg IV		
3	3	5 mg/kg SC		
4	3	20 mg/kg IV		
5	3	40 mg/kg IV		
6	5	5 mg/kg SC	5 mg/kg SC	5 mg/kg SC
7	5	20 mg/kg IV	20 mg/kg IV	20 mg/kg IV
Total	25	More people may be enrolled, if needed, to reach the study goals.		

The study will start by assigning subjects to get the lowest dose of VRC07-523LS in Group 1. If people in the lower dose groups tolerate the study product, the next dose groups may enroll. This pattern will continue until we reach the highest dose. People who are available for 24 weeks of study participation may enroll into Groups 1 to 5. People who are available for 48 weeks of study participation may enroll into Group 6 or Group 7. For Groups 6 and 7 who will get 3 doses of VRC07-523LS, the second and third doses can be given once the first dose is determined to be safe.

If you are female and able to become pregnant, a pregnancy test will be done before each product administration. The result of the test must be negative for you to get study product. You must use an effective method of birth control for the entire study.

- Intravenous (IV) Route Dose Groups:

  If you are in a group getting VRC07-523LS by IV infusion, we will place a thin tube or IV line in a vein on your arm on the day you get the study product. If needed, we will place a second IV line in a vein on your other arm for blood sample collection. VRC07-523LS will be mixed into a bag of liquid called "normal saline" or salt water. The mix of normal saline and VRC07-523LS will be given directly into your vein. A pump will control how fast the study product goes into the vein. The goal is to give it over about 30 minutes or longer. If you have side effects, the rate of the infusion may be slowed down or stopped. At the end of each infusion, we will monitor you for at least four hours and collect blood samples.

  - Blood sample collections for IV Groups:

    On the day of your first IV infusion of VRC07-523LS, we will collect blood samples from you before and right after the infusion, and about 1 hour, 3 hours, and 6 hours after the infusion. You will also be asked to come back to the clinic 1 to 3 times during that first week for sample collection. If you are in Group 7, for the second and third doses of VRC07-523LS, we will collect blood samples from you before and right after the infusion, and then again about 1 hour after the infusion. You will also be asked to come back to the clinic 4-5 times after each repeat dose.

- Subcutaneous (SC) Route Dose Groups:

  If you are in a group getting VRC07-523LS by SC injection, we will put a small needle into the fatty tissue under your skin. The abdominal area is usually where the needle will be inserted in your body. It is possible we may use your arm or thigh area instead. VRC07-523LS will not be mixed with any other liquid. You will get the SC doses by injection with a

standard needle and syringe in 1 to 4 SC sites on your body. After all of the injections are given each time, we will monitor you for at least four hours.

- Blood sample collections for SC Groups:

  On the day of your first SC injection of VRC07-523LS, we will collect blood samples from you before the injection. You will also be asked to come back to the clinic 1 to 3 times during that first week for sample collection. If you are in Group 6, for the second and third doses of VRC07-523LS, we will collect blood samples from you before each injection. You will also be asked to come back to the clinic 4-5 times after each repeat dose.

We will give you a thermometer and ask you to check your temperature every day for 3 days after you get the study product. We will also ask you to record your temperature and any symptoms you may have. You will get a password to a secure website to record this information on an electronic form or "diary." If you prefer, you can use a paper diary instead.

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

At each visit, we will check you for any health changes or problems. We will ask you how you are feeling and if you have taken any medications. We will draw your blood at scheduled study visits, taking about 1 to 9 tubes of blood depending on the visit. We may ask you to come into the clinic for additional blood collection. We will request urine samples at 2 to 6 visits during the study, depending on your group if you are willing. We will tell you right away if any of your test results show a health problem.

We will use some blood samples to study if your body develops an immune response (antibodies) to the study product. These tests are for research purposes only and are not for checking on your health. We will not give you these results. After completing this study, we may invite you to take part in another study for follow-up sample collection.

Experimental studies follow a set schedule. This helps us answer the research questions. Scheduling for your visits allows some flexibility, but it is important that you work with the staff to follow the schedule. You should try to not miss any visits. You might need to have extra clinic visits and laboratory tests if you have health changes that need to be checked.

Collection of Oral Secretion Samples for Research

If you are willing, we will collect samples of the mouth (oral/saliva) for research during 3-6 study visits, depending on your study group. Collection of these samples is encouraged but not required. If you choose to provide such samples, you may change your mind at any time throughout the study. You may choose not to donate these samples but still take part in the study.

Oral samples will be collected with small disposable sponges, similar to a "Q-tip," which are made for this purpose. Each sponge is new and sterile, and is safe for use in sensitive areas of the body.

These samples are collected to see how VRC07-523LS is distributed in your body. They will not be for checking your health and do not replace routine health care.

HIV TESTING AND COUNSELING

As part of your participation in this study, we will provide you with HIV counseling and testing. We will test you for HIV infection and possibly for other infections if needed to check your eligibility for the study. We will tell you how to remain HIV-uninfected and give you prevention resources. If you are infected with HIV, you will not be able to participate in this study. We will tell you what the results mean, how to find care, how to avoid infecting others, how we report HIV infection, and the importance of informing your partners that may be at risk because of your HIV infection.

If you have questions regarding the HIV testing, you are encouraged to discuss them with the study nurse or doctor, or you may call a NIH Clinical Center HIV counselor at 301-496-2381.

MONITORING OF THE STUDY

A group of physicians and scientists at NIH will monitor this study. This group will review the information from the study and will pay close attention to possible harmful reactions. If serious side effects occur, VRC07-523LS administrations may be delayed or canceled.

GENETIC TESTING

Some of the blood drawn from you as part of this study will be used for genetic tests. Some genetic tests are done in research studies to see if genetic differences in people cause different types of immune responses. Your blood sample used in these genetic tests will not have your name on it and the results will not be in your medical record. These tests are not used to check your health and we will not tell you the results.

A special genetic test, called HLA typing, is done by the NIH Clinical Center medical laboratory. These results will be in your medical record but they will not be used to check your health. Any genetic testing, including HLA testing, is for research purposes only. Any genetic information collected or learned about you will be kept confidential. Medical records, including HLA test results, are kept securely. We will not give any genetic information that is in your medical record to anyone without your permission.

STORED SAMPLES

We will collect samples (including blood and possibly oral secretions) from you during the study. We will keep these samples for future research to learn more about monoclonal antibodies, vaccines, the immune system, and/or other medical conditions. Results from research with your samples will not be in your medical record or reported to you.

Labeling of Stored Samples: We will label your stored samples by a special code or number. Only the study team can link this code to you. Any identifying information about you (like name or date of birth) will be kept as confidential as allowable by law. Despite protections, there is a small chance that information identifying you will be given to someone who should not get it.

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

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

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

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

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

POSSIBLE STUDY RISKS

Risks from IV infusions or SC injections: It is possible that you may have some side effects. 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 VRC07-523LS: This study is the first time that VRC07-523LS is being given to people.

VRC07-523LS is similar to the VRC monoclonal antibody, VRC01. More than 150 adults have received one or more doses of VRC01 by IV or SC routes. There were no safety concerns and no concerning reactions to the product. However, VRC07-523LS may have additional unknown risks and side effects.

There are several antibody products that are permitted for use in people. Other antibody products have been given safely by both the IV and the SC route. Local reactions at the site of the SC injections are common, but these reactions are usually mild and resolve in a few days. Most side effects tend to occur within the first 24 hours.

Side effects to study product infusions may include fever, chills, shaking, nausea, vomiting, pain, headache, dizziness, trouble breathing, high or low blood pressure, itchiness, rash, hives, lip or face swelling, diarrhea, racing heart or chest pain. These reactions may be related to how fast the antibody product is given. However, we rarely saw these reactions when VRC01 was given. When reactions were reported, they were usually mild. VRC01 given by the SC route has sometimes caused mild itchiness, redness and/or swelling at site of injection. These symptoms usually cleared within a few minutes to hours after the product was given. In an ongoing study, additional product injections were discontinued for one subject who developed mild chest discomfort and for one subject who developed mild rash that were associated with study product administration (VRC01 or placebo).

We are giving VRC07-523LS at a controlled rate. If symptoms occur while VRC07-523LS is being given, tell the nurse. Slowing or stopping the flow rate may help improve the symptoms.

Some antibody products have a risk of serious allergic reactions that can be life-threatening.

- Anaphylaxis is one type of allergic reaction that may happen soon after an antibody product is given. This reaction can include difficulty breathing, low blood pressure, hives or rash, swelling in the mouth and face.
- Serum sickness is a delayed type of allergic reaction that may happen several days to three weeks after an antibody product is given. This reaction can include hives or rash, fever, enlarged lymph nodes, muscle pains, joint pains, chest discomfort and shortness of breath.

Some antibodies of the type that attack human proteins can increase the risk of serious infections. VRC07-523LS is not expected to increase the risk of serious infections because it attacks a virus and not a human protein.

In addition to the possible risks that are listed above, VRC07-523LS may have other side effects that we do not know about yet. Participation in this study may affect your eligibility for future monoclonal antibody studies. We will give you any new information about risks or other information that becomes available that may affect your decision to continue in the study.

Risks of Blood Drawing: Blood drawing may cause pain and bruising and rarely, may cause a feeling of lightheadedness or fainting. Rarely, it may cause infection at the site where the blood is taken. In this study on the day of an infusion, an IV line may be placed in your vein and left for a few hours. Problems at the IV site are usually mild and may include pain, bruising, minor swelling or bleeding. Rarely, there may be an infection, vein irritation, or a blood clot.

Risks of Oral Mucosa Sample Collection: Collection of samples by swabs and wicks by rubbing them over the mucosal surfaces in the mouth can cause brief discomfort and, rarely, a little bleeding.

Risk of a False Positive HIV Antibody Test Caused by VRC07-523LS: An HIV antibody test is the usual way to test for HIV infection. VRC01 and VRC07-523LS are antibodies against HIV. Based on laboratory testing, VRC01 does not cause a positive HIV antibody test in standard diagnostic tests. Since VRC07-523LS is similar to VRC01, we expect that VRC07-523LS does not cause a positive HIV antibody test. However, we do not know yet if it will cause a positive HIV antibody test or not. We will test for HIV antibodies at some visits. If you ever need or want an HIV test while you are on the study, please ask the VRC Clinic to do the test. We will tell you the results of your HIV test.

Risks during Pregnancy: We do not know what effects VRC07-523LS may have on a fetus or nursing infant. Women who are able to have children must agree to not get pregnant during study participation. We will discuss effective birth control methods with you.

You must notify the clinic staff right away if you get pregnant during this study or think that you might be pregnant. If you get pregnant, you will not get any more VRC07-523LS administrations and we will not collect any more blood for research. However, you will be asked to continue with study follow-up visits to check on your health and to report the outcome of the pregnancy to us, which will be reported to the antiretroviral pregnancy registry (http://www.apregistry.com).

POSSIBLE BENEFITS

This study will not provide you with any direct health benefit. You and others may benefit in the future from the information that we learn from the study.

COSTS TO YOU FOR PARTICIPATION

There are no costs to you for participating in this study. You or your health insurance will have to pay for all medical costs for medical care that you get outside this study.

COMPENSATION TO YOU FOR YOUR PARTICIPATION

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

The compensation is $175 for scheduled visits with blood drawing and oral swabs; $375 for IV product administration visit(s) that includes follow-up blood sample collections on the same day, and $325 for SC product administration visit(s) without follow-up sample collections on the same day. Compensation for timely completion of all 3 days of an electronic diary will be $25 total. Additional compensation for clinic visits that do not include research blood sample collection will be $75. Total compensation for completion of the study is estimated to range from $2475 to $5425 and is based on the number and type of study visits you complete.

You will get your compensation about 2 weeks after each completed visit by direct deposit into a bank account that you specify to the volunteer payment office. Your compensation may need to be reported to the internal revenue service (IRS) as taxable income.

REASONS FOR DISCONTINUING STUDY PRODUCT ADMINISTRATION OR REMOVING YOU FROM THE STUDY

You may be stopped from getting VRC07-523LS for several different reasons, including:

- You don't keep appointments or follow study procedures.
- You get a serious illness that needs ongoing medical care.
- You have a serious side effect thought to be due to VRC07-523LS.
- You enroll in another research study at the same time you are in this study.
- You become pregnant.
- The study is stopped or canceled.

A study may be stopped or canceled by a study sponsor, a regulatory agency or by the study investigators. If this happens, we will tell you the reason why the study was stopped.

You may choose to stop participating in the study at any time. If you got any doses of VRC07-523LS, you will be asked to keep follow-up visits so we can monitor your health. We may stop collecting samples that are for research purposes only.

ALTERNATIVES

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

CONFLICT OF INTEREST

The NIH research staff is checked yearly for conflicts of interest. You may ask the research team for more information. This study may have investigators who are not NIH employees. Non-NIH investigators are expected to follow the principles of the Protocol Review Guide but are not required to report their personal financial holdings to the NIH.

The NIH, including some members of the VRC scientific staff, developed the investigational product being used in this research study. The results of this study could play a role in whether

the FDA will approve the study product for sale at some time in the future. If approved, the future sale of the study product could lead to payments to NIH and some NIH scientists. By U.S. law, government scientists are required to receive such payments for their inventions. You will not receive any money from the development or sale of the product.

Manufacturing process of the investigational product used in this trial is currently not available as a stock option by any commercial entity.

CLINICALTRIALS.GOV

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

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or other authorized people.

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

3. Payments. The amount of payment to research volunteers is guided by the NIH policies. In general, patients are not paid for taking part in research studies at the NIH. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. Problems or Questions. If you have any problems or questions about this study or about any research-related injury, contact the Principal Investigator, Martin Gaudinski, M.D., or the Study Coordinator, [redacted], at [redacted].

If you have any questions about your rights as a research subject, you may call the Clinical Center Patient Representative at [redacted].

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

COMPLETE APPROPRIATE ITEM(S) BELOW:

Adult Study Participant's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

	Time
Signature of Adult Participant	Date
Print Name	

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM XXXXXX THROUGH XXXXXX.

Signature of Investigator/ Person Obtaining Consent	Date	Signature of Witness	Date
Print Name		Print Name	

Appendix II: Contact Information

Appendix III: Schedule of Evaluations

Schedule 1: Groups 1 (1 mg/kg IV), 2 (5 mg/kg IV), 4 (20 mg/kg IV), and 5 (40 mg/kg IV)																			
Visit Number			01R	02	02A	02B	02C	02D	03	04	06	07	08	09	10	11	15	16	17
Time After Infusion				Pre	EOI	1hr	3h	6h	24hr	48hr	Wk1	Wk2	Wk3	Wk4	Wk8	Wk12	Wk16	Wk20	Wk24
[1]Day of Study			-42 to -1	D0	D0	D0	D0	D0	D1	D2	D7	D14	D21	D28	D56	D84	D112	D140	D168
Clinical	Tube	Screen	Enroll	Day of infusion															
VRC 500 Screening Consent		X																	
VRC 605 AoU; Consent			X																
[2] Screen: Physical exam, ht, wt; Other: targeted exam, BP, pulse, temp; also wt at visit 02		X	X	X	X				X	X	X	X	X	X	X	X	X	X	X
Complete med history at screen; then interim med history		X	X	X					X	X	X	X	X	X	X	X	X	X	X
[3]VRC07-523LS Administration				X															
Begin 3-day Diary Card				X															
CBC / differential	EDTA	3		3					3		3	3		3					
[4]ALT, AST, ALP, creatinine (total bili, BUN, albumin, protein, calcium, Na, K, Cl, CO2, glucose)	GLT	4		4					4		4	4		4					
Urine protein		X		X								X							
[5]Pregnancy test: urine or serum		X	X	X								X					X		X
[5]Pregnancy prevention counseling/ Reproductive Information Form		X	X	X								X					X		X
HIV EIA (other tests, if needed)	SST	4									4								
HIV prevention counseling		X		X							X							X	
[6]HLA type	EDTA															20			
Research Samples																			
Timed PK samples	SST			4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
[7]Oral sample			[X]								[X]					[X]			
PBMC and plasma	EDTA	20	20											20					
Serum	SST	24	24	16						16	16	16	16	16	16	16	16	16	16
Daily Volume (mL)		**55**	**44**	**27**	**4**	**4**	**4**	**4**	**11**	**20**	**31**	**27**	**20**	**47**	**20**	**40**	**20**	**20**	**20**
Cumulative Volume (mL)		**55**	**99**	**126**	**130**	**134**	**138**	**142**	**153**	**173**	**204**	**231**	**251**	**298**	**318**	**358**	**378**	**398**	**418**

[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, height (ht) and weight (wt). At other visits, if medically indicated, a targeted exam is performed. Otherwise only blood pressure (BP), pulse, and temperature 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. All subjects will be observed for 4 hours after each product administration.

[4] ALT, AST, ALP and creatinine will be collected at all scheduled timepoints. Comprehensive metabolic panel (CMP) will be collected at screening, baseline, and 2 weeks after each product administration and as needed at additional timepoints.

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

[6] HLA type blood sample is collected once at any timepoint in the study and is shown as a Visit 11 evaluation for convenience; however, if HLA type is already available in the medical record it does not need to be repeated. HLA type may also be obtained from a frozen sample.

[7] Oral mucosa sample collection is encouraged but not mandatory. Oral samples will not be collected for Group 1. [X] indicates optional, as needed.

Visit windows: Visits 02A, 02B and 02C (±10 min); Visit 02D (-2 hrs), Visits 03, 04 (± 6 hrs); Visits 06, 07, 08, 09 (±2 days), and Visits 10, 11, 15, 16 and 17 (±7 days).
Visits 05, 12, 13 and 14 are not applicable to Schedule 1.

Schedule 2: Group 3 (5 mg/kg SC)																
Visit Number			01R	02	02A	03	04	05	06	07	08	09	10	11	15	16	17
Time After Infusion				Pre	EOI	24hr	48hr	72hr	Wk1	Wk2	Wk3	Wk4	Wk8	Wk12	Wk16	Wk20	Wk24
[1]Day of Study			-42 to -1	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 605 AoU; Consent			X														
[2]Screen: Physical exam, ht, wt; Other: targeted exam, BP, pulse, temp; also wt at visit 02		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete med history at screen; then interim med history		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
[3]VRC07-523LS Administration				X													
Begin 3-day Diary Card				X													
CBC / differential	EDTA	3		3		3			3	3		3					
[4]ALT, AST, ALP, creatinine (total bili, BUN, albumin, protein, calcium, Na, K, Cl, CO2, glucose)	GLT	4		4		4			4	4		4					
Urine protein		X		X						X							
[5]Pregnancy test: urine or serum		X	X	X						X					X		X
[5]Pregnancy prevention counseling/ Reproductive Information Form		X	X	X						X					X		X
HIV EIA (other tests, if needed)	SST	4						4									
HIV prevention counseling		X		X				X								X	
[6]HLA type	EDTA													20			
Research Samples																	
Timed PK samples	SST			4		4	4	4	4	4	4	4	4	4	4	4	4
[7]Oral sample			[X]						[X]					[X]			
PBMC and plasma	EDTA	20	20									20					
Serum	SST	24	24	16			16	16	16	16	16	16	16	16	16	16	16
Daily Volume (mL)		**55**	**44**	**27**	**0**	**11**	**20**	**24**	**27**	**27**	**20**	**47**	**20**	**40**	**20**	**20**	**20**
Cumulative Volume (mL)		**55**	**99**	**126**	**126**	**137**	**157**	**181**	**208**	**235**	**255**	**302**	**322**	**362**	**382**	**402**	**422**

[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, height (ht) and weight (wt). At other visits, if medically indicated, a targeted exam is performed. Otherwise only blood pressure (BP), pulse, and temperature 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. All subjects will be observed for 4 hours after each product administration.

[4] ALT, AST, ALP and creatinine will be collected at all scheduled timepoints. Comprehensive metabolic panel (CMP) will be collected at screening, baseline, and 2 weeks after each product administration and as needed at additional timepoints.

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

[6] HLA type blood sample is collected once at any timepoint in the study and is shown as a Visit 11 evaluation for convenience; however, if HLA type is already available in the medical record it does not need to be repeated. HLA type may also be obtained from a frozen sample.

[7] Oral mucosa sample collection is encouraged but not mandatory. [X] indicates optional, as needed.

Visit windows: Visit 02A (±10 min); Visits 03, 04, 05 (± 6 hrs); Visits 06, 07, 08, 09 (±2 days); Visits 10, 11, 15, 16, 17 (±7 days). Visits 12-14 are not applicable to Schedule 2.

Schedule 3: Group 6 (5 mg/kg SC by repeat dosing)																							
Visit Number			01R	02	02A	03	04	05	06	07	09	10	11	11A	11E	12	13	14	15	16	17	17A	17E
Time After Infusion				Pre D0	EOI D0	24hr	48h	72hr	1wk	Wk2	Wk4	Wk8	Pre Wk12	EOI Wk12	24hr	72hr	Wk13	Wk14	Wk16	Wk20	Pre Wk24	EOI Wk24	24hr
[1]Day of Study			-42 to -1	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 605 AoU; Consent			X																				
[2]Screen: Physical exam, ht, wt; Other: targeted exam, BP, pulse, temp; wt at visits 02, 11, and 17		X	X	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]VRC07-523LS Administration				X									X								X		
Begin 3-day Diary Card				X									X								X		
Phone contact; clinic visit if indicated															X								X
CBC / diff	EDTA	3		3		3			3	3		3	3			3	3	3		3	3		
[4]ALT, AST, ALP, creatinine (total bili, BUN, albumin, protein, calcium, Na, K, Cl, CO2, glucose)	GLT	4		4		4			4	4		4	4			4	4	4		4	4		
Urine protein		X		X						X			X					X			X		
[5]Pregnancy test: urine or serum		X	X	X						X			X					X			X		
[5]Pregnancy prevention counseling/ Reproductive Information Form		X	X	X						X			X					X			X		
HIV EIA (other tests, if needed)	SST	4						4								4							
HIV prevention counseling		X		X				X					X			X					X		
Research Samples																							
Timed PK samples	SST			4		4	4	4	4	4	4	4	4			4	4	4	4	4	4		
[6]Oral sample			[X]										[X]								[X]		
PBMC and plasma	EDTA	20	20																				
Serum	SST	24	24	16			16	16	16	16	16	16	16				16	16	16	16	16		
Daily Volume (mL)		**55**	**44**	**27**	**0**	**11**	**20**	**24**	**27**	**27**	**20**	**27**	**27**	**0**	**0**	**15**	**27**	**27**	**20**	**27**	**27**	**0**	**0**
Cumulative Volume (mL)		**55**	**99**	**126**	**126**	**137**	**157**	**181**	**208**	**235**	**255**	**282**	**309**	**309**	**309**	**324**	**351**	**378**	**398**	**425**	**452**	**452**	**452**

[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, height (ht) and weight (wt). At other visits, if medically indicated, a targeted exam is performed. Otherwise only blood pressure (BP) and temperature are required, except at Visits 02, 11, and 17 when 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. All subjects will be observed for 4 hours after each product administration.

[4] ALT, AST, ALP and creatinine will be collected at all scheduled timepoints. Comprehensive metabolic panel (CMP) will be collected at screening, baseline, and 2 weeks after each product administration and as needed at additional timepoints.

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

[6] Oral mucosa sample collection is encouraged but not mandatory. [X] indicates optional, as needed.

*Subjects who discontinue product administration may be followed weekly for 4 weeks, then monthly for 24 weeks after last administration, per Schedule 3 (continued).

Visit windows: Visit A (±10 min); Visit E (+ 1 day); Visits 03, 04, 05, 12, and 18 (± 6 hrs); Visits 06, 07, 13, and 14 (±2 days); Visits 09, 10, 11, 15, 16 and 17 (±7 days, with not less than 21 days between injections). Visits 08, 11B, 11C, 17B, and 17C are not applicable to Schedule 3.

Schedule 3 (continued): Group 6 (5 mg/kg SC by repeat dosing)											
Visit Number*		18	19	20	21	22	23	24	25	26	27
Time After Infusion		72hr	Wk25	Wk26	Wk27	Wk28	Wk32	Wk36	Wk40	Wk44	Wk48
Day of Study		D171	D175	D182	D189	D196	D224	D252	D280	D308	D336
Clinical	Tube										
Targeted physical exam, BP, pulse, temp		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
CBC / diff	EDTA	3	3	3		3					
[1]ALT, AST, ALP, creatinine (total bili, BUN, albumin, protein, calcium, Na, K, Cl, CO2, glucose)	GLT	4	4	4		4					
Urine protein				X							
Pregnancy test: urine or serum				X				X			X
[2]Pregnancy prevention counseling / Reproductive Information Form				X				X			X
HIV EIA (other tests, if needed)	SST	4									
HIV prevention counseling		X						X			
[3]HLA type	EDTA			20							
Research Samples											
Timed PK samples	SST	4	4	4	4	4	4	4	4	4	4
[4]Oral sample						[X]			[X]		[X]
PBMC and plasma	EDTA			20							
Serum	SST		16	16	16	16	16	16	16	16	16
Daily Volume (mL)		**15**	**27**	**67**	**20**	**27**	**20**	**20**	**20**	**20**	**20**
Cumulative Volume (mL)		**467**	**494**	**561**	**581**	**608**	**628**	**648**	**668**	**688**	**708**

[1] ALT, AST, ALP and creatinine will be collected at all scheduled timepoints. Comprehensive metabolic panel (CMP) will be collected at screening, baseline, and 2 weeks after each product administration and as needed at additional timepoints

[2] Complete a Reproductive Information Form when pregnancy test is given.

[3] HLA type blood sample is collected once at any timepoint in the study and is shown as a Visit 20 evaluation for convenience; however, if HLA type is already available in the medical record it does not need to be repeated. HLA type may also be obtained from a frozen sample.

[4] Oral mucosa sample collection is encouraged but not mandatory. [X] indicates optional, as needed.

* Subjects who discontinue product administration may be followed weekly for 4 weeks, then monthly for 24 weeks after last injection, per Schedule 3 (continued).

Visit windows: Visit 18 (± 6 hrs), Visits 19-22 (±2 days), and Visits 23-27 (±7 days).

Schedule 4: Group 7 (20 mg/kg IV by repeat dosing)																										
Visit Number			01R	02	02A	02B	02C	02D	03	04	06	07	09	10	11	11A	11B	11E	12	13	14	15	16	17	17A	17B
Time After Day 0 Infusion				Pre D0	EOI D0	1hr	3h	6h	24hr	48h	Wk1	Wk2	Wk4	Wk8	Pre Wk12	EOI Wk12	1hr	24hr	72hr	Wk13	Wk14	Wk16	Wk20	Pre Wk24	EOI Wk24	1hr
[1]Day of Study			-42 to -1	D0	D0	D0	D0	D0	D1	D2	D7	D14	D28	D56	D84	D84	D84	D85	D87	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 605 AoU; Consent			X																							
[2]Screen: Physical exam, ht, wt; Other: targeted exam, BP, pulse, temp; also wt at visits 02, 11, 17		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]VRC07-523LS Administration				X											X									X		
Begin 3-day Diary Card				X											X									X		
Phone contact; clinic visit if indicated																		X								
CBC / diff	EDTA	3		3					3		3	3		3	3				3	3	3		3	3		
[4]ALT, AST, ALP, creatinine (total bili, BUN, albumin, protein, calcium, Na, K, Cl, CO2, glucose)	GLT	4		4					4		4	4		4	4				4	4	4		4	4		
Urine protein		X		X								X			X						X			X		
[5]Pregnancy test: urine or serum		X	X	X								X			X						X			X		
[5]Pregnancy prevention counseling/ Reproductive Information Form		X	X	X								X			X						X			X		
HIV EIA (other tests, if needed)	SST	4									4									4						
HIV prevention counseling		X		X							X				X					X				X		
Research Samples																										
Timed PK samples	SST			4	4	4	4	4	4	4	4	4	4	4	4	4	4			4	4	4	4	4	4	4
[6]Oral sample (all participants)			[X]												[X]									[X]		
PBMC and plasma	EDTA	20	20																							
Serum	SST	24	24	16						16	16	16	16	16	16					16	16	16	16	16		
Daily Volume (mL)		**55**	**44**	**27**	**4**	**4**	**4**	**4**	**11**	**20**	**31**	**27**	**20**	**27**	**27**	**4**	**4**	**0**	**7**	**31**	**27**	**20**	**27**	**27**	**4**	**4**
Cumulative Volume (mL)		**55**	**99**	**126**	**130**	**134**	**138**	**142**	**153**	**173**	**204**	**231**	**251**	**278**	**305**	**309**	**313**	**313**	**320**	**351**	**378**	**398**	**425**	**452**	**456**	**460**

[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, height (ht) and weight (wt). At other visits, if medically indicated, a targeted exam is performed. Otherwise only blood pressure (BP), pulse, and temperature are required, except at Visits 02, 11, and 17 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. All subjects will be observed for 4 hours after each product administration.

[4] ALT, AST, ALP and creatinine will be collected at all scheduled timepoints. Comprehensive metabolic panel (CMP) will be collected at screening, baseline, and 2 weeks after each product administration and as needed at additional timepoints.

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

[6] Oral mucosa sample collection is encouraged but not mandatory. [X] indicates optional, as needed.

*Subjects who discontinue product administration may be followed weekly for 4 weeks, then monthly for 24 weeks after last administration, per Schedule 4 (continued).

Visit windows: Visits A, B, and C (±10 min); Visit 02D (-2 hrs); Visit E (+1 day); Visits 03, and 04 (±6 hrs); Visits 06, 07, 13, and 14 (±2 days); Visit 12 (+2 days), Visits 09, 10, 11, 15, 16 and 17 (±7 days, with not less than 21 days between infusions). Visits 05, 08, and 18 are not applicable to Schedule 4.

Schedule 4 (continued): Group 7 (20 mg/kg IV by repeat dosing)												
Visit Number*		17E	18	19	20	21	22	23	24	25	26	27
Time After Infusion		24hr	72hr	Wk25	Wk26	Wk27	Wk28	Wk32	Wk36	Wk40	Wk44	Wk48
Day of Study		D169	D171	D175	D182	D189	D196	D224	D252	D280	D308	D336
Clinical	Tube											
Targeted physical exam, BP, pulse, temp		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
Phone contact; clinic visit if indicated		X										
CBC / diff	EDTA		3	3	3		3	3				
[1]ALT, AST, ALP, creatinine (total bili, BUN, albumin, protein, calcium, Na, K, Cl, CO2, glucose)	GLT		4	4	4		4	4				
Urine protein					X							
Pregnancy test: urine or serum					X				X			X
[2]Pregnancy prevention counseling / Reproductive Information Form					X				X			X
HIV EIA (other tests, if needed)	SST			4								
HIV prevention counseling				X					X			
[3]HLA type	EDTA				20							
Research Samples												
Timed PK samples	SST			4	4	4	4	4	4	4	4	4
[4]Oral sample							[X]			[X]		[X]
PBMC and plasma	EDTA				20							
Serum	SST			16	16	16	16	16	16	16	16	16
Daily Volume (mL)		**0**	**7**	**31**	**67**	**20**	**27**	**27**	**20**	**20**	**20**	**20**
Cumulative Volume (mL)		**460**	**467**	**498**	**565**	**585**	**612**	**639**	**659**	**679**	**699**	**719**

[1] ALT, AST, ALP and creatinine will be collected at all scheduled timepoints. Comprehensive metabolic panel (CMP) will be collected at screening, baseline, and 2 weeks after each product administration and as needed at additional timepoints.
[2] Complete a Reproductive Information Form when pregnancy test is given.
[3] HLA type blood sample is collected once at any timepoint in the study and is shown as a Visit 20 evaluation for convenience; however, if HLA type is already available in the medical record, it does not need to be repeated. HLA type may also be obtained from a frozen sample.
[4] Oral mucosa sample collection is encouraged but not mandatory. [X] indicates optional, as needed.
*Subjects who discontinue product administration may be followed weekly for 4 weeks, then monthly for 24 weeks after last infusion, per Schedule 4 (continued).
Visit windows: Visit 17E (+1 day); Visit 18 (+2 days), Visits 19-22 (±2 days), and Visits 23-27 (±7 days).

Appendix IV: Table for Grading Severity of Adverse Events

The U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0. [November 2014] will be used in this study. The table is available at the following link:

http://rsc.tech-res.com/docs/default-source/safety/daids_ae_grading_table_v2_nov2014.pdf?sfvrsn=8

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

- Weight loss will be recorded as an AE only if it is considered deleterious to the participant's health.
- For severity grading of the solicited bruising parameter at the product administration site, the definitions based on size of the largest diameter and listed for the "Injection Site Erythema or Redness" will be used. The severity grade definition for "Bruising" provided under the Dermatologic Clinical Conditions will be used only for unsolicited AEs involving bruising at other body locations.

INSTITUTE: National Institute of Allergy and Infectious Diseases

STUDY NUMBER: 17-I-0030 PRINCIPAL INVESTIGATOR: Martin Gaudinski, M.D.

STUDY TITLE: VRC 605: A Phase 1 Dose-Escalation Study of the Safety and Pharmacokinetics of a Human Monoclonal Antibody, VRC-HIVMAB075-00-AB (VRC07-523LS), Administered Intravenously or Subcutaneously to Healthy Adults

Initial Review Approved by the IRB on 12/13/16
Amendment Approved by the IRB on 08/15/17 (E) Date Posted to Web: 08/22/17
Study Consent, [Version 3.0]

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

PURPOSE AND PLAN OF THE STUDY

This is the study of an experimental product called "VRC07-523LS." The U.S. Food and Drug Administration (FDA) allows it to be used for research only. VRC07-523LS is an antibody directed against HIV virus. The human body uses antibodies as one way to help fight infection. There is currently no cure for HIV or vaccine to prevent it.

The main purpose of this study is to see if the experimental product is safe and well-tolerated. We will study the amount of VRC07-523LS in the body and how it changes over time. We will check to see if people who get VRC07-523LS make an immune response (antibody) to it.

About 25 to 40 people will participate in this study at the NIH Clinical Center in Bethesda, Maryland. The study will have about 13-27 clinic visits over 24-48 weeks for each person, depending on the study group.

STUDY PRODUCT

VRC07-523LS is a monoclonal antibody or "MAb." An antibody is a protein that is used by the immune system to find and block bacteria and viruses, like HIV. Monoclonal means that all the antibodies in the product are the same.

The formal name for the product is VRC-HIVMAB075-00-AB. VRC07-523LS is a human antibody but it is a genetically modified synthetic product. It was made based on an antibody that was first found in an HIV-infected person. Although the antibody was found in a human, the product is not made by collecting it from a human.

VRC07-523LS was developed by the Vaccine Research Center (VRC) at NIH. This product was made in a drug manufacturing laboratory. This is the first study to give VRC07-523LS to humans.

VRC07-523LS is similar to the monoclonal antibody VRC01 and was manufactured in a similar way. VRC01 has been given to over 150 healthy and HIV-infected adults and has been found to be safe and well-tolerated.

VRC07-523LS will not protect you from HIV infection. Because we have never tested this product in humans, we assume that it cannot protect against HIV infection. You cannot get HIV from VRC07-523LS because there are no parts of HIV in it.

In laboratory and animal studies, VRC07-523LS was shown to attach to and inactivate many types of HIV viruses. We do not know if the product will act the same way when given to humans. It will take many studies to learn if the product will be useful for preventing or treating HIV. This study alone will not answer this question.

ELIGIBILITY

You are eligible to participate in this study because you have completed the screening process and are known to be the following:

- 18 to 50 years old
- In general good health without significant medical problems as determined at screening
- Willing to get VRC07-523LS
- Willing to donate blood samples for future research
- Willing to be tested for HIV infection
- If female and able to get pregnant: willing to use birth control for the whole study.

STUDY PROCEDURES

The study will have 7 groups. Each group will have about 3-5 people in it. The groups are defined by the dose of VRC07-523LS and how it is given. Most people will get VRC07-523LS by the intravenous (IV) route, meaning into a vein. Some people will get VRC07-523LS by the subcutaneous (SC) route, meaning into the fatty tissue under the skin. Both methods use a needle. The product administration visit(s) will last about 8 hours. Other clinic visits will take about 2 hours.

The study will last about 24 weeks for people in Groups 1-5 because they will only get the study product one time. The study will last for about 48 weeks for people in Groups 6 and 7 because they will get the study product three times.

People in Groups 1-5 will get different doses of the study product 1 time so we can see how long it lasts in the body and if higher doses are safe.

People in Groups 6 and 7 will get the study product 3 times instead of 1 time so we can see if repeat doses are better. We also want to see if it is better to give the study product by the IV or SC routes. This information will be helpful for future uses of the product.

If you agree to take part in this study, you will get 1 or 3 doses of VRC07-523LS, depending on the group. You will know how many doses you will get once you enroll. The amount of study product you will get is calculated based on your body weight. We will measure your weight on the day the study product is given to calculate the dose.

The Study Groups are shown in the following table:

Group	Subjects	Schedule		
		Day 0	Week 12	Week 24
1	3	1 mg/kg IV		
2	3	5 mg/kg IV		
3	3	5 mg/kg SC		
4	3	20 mg/kg IV		
5	3	40 mg/kg IV		
6	5	5 mg/kg SC	5 mg/kg SC	5 mg/kg SC
7	5	20 mg/kg IV	20 mg/kg IV	20 mg/kg IV
Total	25	More people may be enrolled, if needed, to reach the study goals.		

The study will start by assigning subjects to get the lowest dose of VRC07-523LS in Group 1. If people in the lower dose groups tolerate the study product, the next dose groups may enroll. This pattern will continue until we reach the highest dose. People who are available for 24 weeks of study participation may enroll into Groups 1 to 5. People who are available for 48 weeks of study participation may enroll into Group 6 or Group 7. For Groups 6 and 7 who will get 3 doses of VRC07-523LS, the second and third doses can be given once the first dose is determined to be safe.

If you are female and able to become pregnant, a pregnancy test will be done before each product administration. The result of the test must be negative for you to get study product. You must use an effective method of birth control for the entire study.

- Intravenous (IV) Route Dose Groups:

  If you are in a group getting VRC07-523LS by IV infusion, we will place a thin tube or IV line in a vein on your arm on the day you get the study product. If needed, we will place a second IV line in a vein on your other arm for blood sample collection. VRC07-523LS will be mixed into a bag of liquid called "normal saline" or salt water. The mix of normal saline and VRC07-523LS will be given directly into your vein. A pump will control how fast the study product goes into the vein. The goal is to give it over about 30 minutes or longer. If you have side effects, the rate of the infusion may be slowed down or stopped. At the end of each infusion, we will monitor you for at least four hours and collect blood samples.

  - Blood sample collections for IV Groups:

    On the day of your first IV infusion of VRC07-523LS, we will collect blood samples from you before and right after the infusion, and about 1 hour, 3 hours, and 6 hours after the infusion. You will also be asked to come back to the clinic 1 to 3 times during that first week for sample collection. If you are in Group 7, for the second and third doses of VRC07-523LS, we will collect blood samples from you before and right after the infusion, and then again about 1 hour after the infusion. You will also be asked to come back to the clinic 4-5 times after each repeat dose.

- Subcutaneous (SC) Route Dose Groups:

  If you are in a group getting VRC07-523LS by SC injection, we will put a small needle into the fatty tissue under your skin. The abdominal area is usually where the needle will be inserted in your body. It is possible we may use your arm or thigh area instead. VRC07-523LS will not be mixed with any other liquid. You will get the SC doses by injection with a standard needle and syringe in 1 to 4 SC sites on your body. After all of the injections are given each time, we will monitor you for at least four hours.

  - Blood sample collections for SC Groups:

    On the day of your first SC injection of VRC07-523LS, we will collect blood samples from you before the injection. You will also be asked to come back to the clinic 1 to 3 times during that first week for sample collection. If you are in Group 6, for the second and third doses of VRC07-523LS, we will collect blood samples from you before each injection. You will also be asked to come back to the clinic 4-5 times after each repeat dose.

We will give you a thermometer and ask you to check your temperature every day for 3 days after you get the study product. We will also ask you to record your temperature and any symptoms you may have. You will get a password to a secure website to record this information on an electronic form or "diary." If you prefer, you can use a paper diary instead.

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

At each visit, we will check you for any health changes or problems. We will ask you how you are feeling and if you have taken any medications. We will draw your blood at scheduled study visits, taking about 1 to 9 tubes of blood depending on the visit. We may ask you to come into the clinic for additional blood collection. We will request urine samples at 2 to 6 visits during the study, depending on your group if you are willing. We will tell you right away if any of your test results show a health problem.

We will use some blood samples to study if your body develops an immune response (antibodies) to the study product. These tests are for research purposes only and are not for checking on your health. We will not give you these results. After completing this study, we may invite you to take part in another study for follow-up sample collection.

Experimental studies follow a set schedule. This helps us answer the research questions. Scheduling for your visits allows some flexibility, but it is important that you work with the staff to follow the schedule. You should try to not miss any visits. You might need to have extra clinic visits and laboratory tests if you have health changes that need to be checked.

COLLECTION OF ORAL SECRETION SAMPLES FOR RESEARCH

If you are willing, we will collect samples of the mouth (oral/saliva) for research during 3-6 study visits, depending on your study group. Collection of these samples is encouraged but not required. If you choose to provide such samples, you may change your mind at any time throughout the study. You may choose not to donate these samples but still take part in the study.

Oral samples will be collected with small disposable sponges, similar to a "Q-tip," which are made for this purpose. Each sponge is new and sterile, and is safe for use in sensitive areas of the body.

These samples are collected to see how VRC07-523LS is distributed in your body. They will not be for checking your health and do not replace routine health care.

HIV TESTING AND COUNSELING

As part of your participation in this study, we will provide you with HIV counseling and testing. We will test you for HIV infection and possibly for other infections if needed to check your eligibility for the study. We will tell you how to remain HIV-uninfected and give you prevention resources. If you are infected with HIV, you will not be able to participate in this study. We will tell you what the results mean, how to find care, how to avoid infecting others, how we report HIV infection, and the importance of informing your partners that may be at risk because of your HIV infection.

If you have questions regarding the HIV testing, you are encouraged to discuss them with the study nurse or doctor, or you may call a NIH Clinical Center HIV counselor at .

MONITORING OF THE STUDY

A group of physicians and scientists at NIH will monitor this study. This group will review the information from the study and will pay close attention to possible harmful reactions. If serious side effects occur, VRC07-523LS administrations may be delayed or canceled.

GENETIC TESTING

Some of the blood drawn from you as part of this study will be used for genetic tests. Some genetic tests are done in research studies to see if genetic differences in people cause different types of immune responses. Your blood sample used in these genetic tests will not have your name on it and the results will not be in your medical record. These tests are not used to check your health and we will not tell you the results.

A special genetic test, called HLA typing, is done by the NIH Clinical Center medical laboratory. These results will be in your medical record but they will not be used to check your health. Any genetic testing, including HLA testing, is for research purposes only. Any genetic information collected or learned about you will be kept confidential. Medical records, including HLA test results, are kept securely. We will not give any genetic information that is in your medical record to anyone without your permission.

STORED SAMPLES

We will collect samples (including blood and possibly oral secretions) from you during the study. We will keep these samples for future research to learn more about monoclonal antibodies, vaccines, the immune system, and/or other medical conditions. Results from research with your samples will not be in your medical record or reported to you.

Labeling of Stored Samples: We will label your stored samples by a special code or number. Only the study team can link this code to you. Any identifying information about you (like name or date of birth) will be kept as confidential as allowable by law. Despite protections, there is a small chance that information identifying you will be given to someone who should not get it.

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

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

Any future research studies using your samples will be conducted in a way that protects the rights and privacy of study participants. Your stored samples will be used only for research and will not be sold. The research done with your materials may be used to develop new products in the future but you will not receive payment for such products.

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

POSSIBLE STUDY RISKS

Risks from IV infusions or SC injections: It is possible that you may have some side effects. 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 VRC07-523LS: This study is the first time that VRC07-523LS is being given to people.

VRC07-523LS is similar to the VRC monoclonal antibody, VRC01. More than 150 adults have received one or more doses of VRC01 by IV or SC routes. There were no safety concerns and no concerning reactions to the product. However, VRC07-523LS may have additional unknown risks and side effects.

There are several antibody products that are permitted for use in people. Other antibody products have been given safely

by both the IV and the SC route. Local reactions at the site of the SC injections are common, but these reactions are usually mild and resolve in a few days. Most side effects tend to occur within the first 24 hours.

Side effects to study product infusions may include fever, chills, shaking, nausea, vomiting, pain, headache, dizziness, trouble breathing, high or low blood pressure, itchiness, rash, hives, lip or face swelling, diarrhea, racing heart or chest pain. These reactions may be related to how fast the antibody product is given. However, we rarely saw these reactions when VRC01 was given. When reactions were reported, they were usually mild. VRC01 given by the SC route has sometimes caused mild itchiness, redness and/or swelling at site of injection. These symptoms usually cleared within a few minutes to hours after the product was given. In an ongoing study, additional product injections were discontinued for one subject who developed mild chest discomfort and for one subject who developed mild rash that were associated with study product administration (VRC01 or placebo).

We are giving VRC07-523LS at a controlled rate. If symptoms occur while VRC07-523LS is being given, tell the nurse. Slowing or stopping the flow rate may help improve the symptoms.

Some antibody products have a risk of serious allergic reactions that can be life-threatening.

- Anaphylaxis is one type of allergic reaction that may happen soon after an antibody product is given. This reaction can include difficulty breathing, low blood pressure, hives or rash, swelling in the mouth and face.
- Serum sickness is a delayed type of allergic reaction that may happen several days to three weeks after an antibody product is given. This reaction can include hives or rash, fever, enlarged lymph nodes, muscle pains, joint pains, chest discomfort and shortness of breath.

Some antibodies of the type that attack human proteins can increase the risk of serious infections. VRC07-523LS is not expected to increase the risk of serious infections because it attacks a virus and not a human protein.

In addition to the possible risks that are listed above, VRC07-523LS may have other side effects that we do not know about yet. Participation in this study may affect your eligibility for future monoclonal antibody studies. We will give you any new information about risks or other information that becomes available that may affect your decision to continue in the study.

Risks of Blood Drawing: Blood drawing may cause pain and bruising and rarely, may cause a feeling of lightheadedness or fainting. Rarely, it may cause infection at the site where the blood is taken. In this study on the day of an infusion, an IV line may be placed in your vein and left for a few hours. Problems at the IV site are usually mild and may include pain, bruising, minor swelling or bleeding. Rarely, there may be an infection, vein irritation, or a blood clot.

Risks of Oral Mucosa Sample Collection: Collection of samples by swabs and wicks by rubbing them over the mucosal surfaces in the mouth can cause brief discomfort and, rarely, a little bleeding.

Risk of a False Positive HIV Antibody Test Caused by VRC07-523LS: An HIV antibody test is the usual way to test for HIV infection. VRC01 and VRC07-523LS are antibodies against HIV. Based on laboratory testing, VRC01 does not cause a positive HIV antibody test in standard diagnostic tests. Since VRC07-523LS is similar to VRC01, we expect that VRC07-523LS does not cause a positive HIV antibody test. However, we do not know yet if it will cause a positive HIV antibody test or not. We will test for HIV antibodies at some visits. If you ever need or want an HIV test while you are on the study, please ask the VRC Clinic to do the test. We will tell you the results of your HIV test.

Risks during Pregnancy: We do not know what effects VRC07-523LS may have on a fetus or nursing infant. Women who are able to have children must agree to not get pregnant during study participation. We will discuss effective birth control methods with you.

You must notify the clinic staff right away if you get pregnant during this study or think that you might be pregnant. If you get pregnant, you will not get any more VRC07-523LS administrations and we will not collect any more blood for research. However, you will be asked to continue with study follow-up visits to check on your health and to report the outcome of the pregnancy to us, which will be reported to the antiretroviral pregnancy registry (http://www.apregistry.com).

POSSIBLE BENEFITS

This study will not provide you with any direct health benefit. You and others may benefit in the future from the information that we learn from the study.

COSTS TO YOU FOR PARTICIPATION

There are no costs to you for participating in this study. You or your health insurance will have to pay for all medical costs for medical care that you get outside this study.

COMPENSATION TO YOU FOR YOUR PARTICIPATION

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

The compensation is $175 for scheduled visits with blood drawing and oral swabs; $375 for IV product administration visit(s) that includes follow-up blood sample collections on the same day, and $325 for SC product administration visit(s) without follow-up sample collections on the same day. Compensation for timely completion of all 3 days of an electronic diary will be $25 total. Additional compensation for clinic visits that do not include research blood sample collection will be $75. Total compensation for completion of the study is estimated to range from $2475 to $5425 and is based on the number and type of study visits you complete.

You will get your compensation about 2 weeks after each completed visit by direct deposit into a bank account that you specify to the volunteer payment office. Your compensation may need to be reported to the internal revenue service (IRS) as taxable income.

REASONS FOR DISCONTINUING STUDY PRODUCT ADMINISTRATION OR REMOVING YOU FROM THE STUDY

You may be stopped from getting VRC07-523LS for several different reasons, including:

- You don't keep appointments or follow study procedures.
- You get a serious illness that needs ongoing medical care.
- You have a serious side effect thought to be due to VRC07-523LS.
- You enroll in another research study at the same time you are in this study.
- You become pregnant.
- The study is stopped or canceled.

A study may be stopped or canceled by a study sponsor, a regulatory agency or by the study investigators. If this happens, we will tell you the reason why the study was stopped.

You may choose to stop participating in the study at any time. If you got any doses of VRC07-523LS, you will be asked to keep follow-up visits so we can monitor your health. We may stop collecting samples that are for research purposes only.

ALTERNATIVES

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

CONFLICT OF INTEREST

The NIH research staff is checked yearly for conflicts of interest. You may ask the research team for more information. This study may have investigators who are not NIH employees. Non-NIH investigators are expected to follow the principles of the Protocol Review Guide but are not required to report their personal financial holdings to the NIH.

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

Manufacturing process of the investigational product used in this trial is currently not available as a stock option by any commercial entity.

CLINICALTRIALS.GOV

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

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or other authorized people.

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

3. Payments. The amount of payment to research volunteers is guided by the NIH policies. In general, patients are not paid for taking part in research studies at the NIH. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. Problems or Questions. If you have any problems or questions about this study or about any research-related injury, contact the Principal Investigator, Martin Gaudinski, M.D.., or the Study Coordinator, at .

If you have any questions about your rights as a research subject, you may call the Clinical Center Patient Representative at .

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

COMPLETE APPROPRIATE ITEM(S) BELOW:

Adult Study Participant's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

	Time
Signature of Adult Participant	Date
Print Name	

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM DECEMBER 13, 2016 THROUGH DECEMBER 12, 2017.

Signature of Investigator/ Person Obtaining Consent	Date	Signature of Witness	Date
Print Name		Print Name	