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# VACCINE RESEARCH CENTER
# AIDS CLINICAL TRIALS GROUP

## Protocol VRC 607/ACTG A5378
## (NIH 16-I-0147)
## (DAIDS-ES ID 30089)

## A PHASE 1, SINGLE DOSE STUDY OF THE SAFETY AND VIROLOGIC EFFECT OF AN HIV-1 SPECIFIC BROADLY NEUTRALIZING HUMAN MONOCLONAL ANTIBODY, VRC-HIVMAB080-00-AB (VRC01LS) OR VRC-HIVMAB075-00-AB (VRC07-523LS), ADMINISTERED INTRAVENOUSLY TO HIV-INFECTED 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)**
**Bethesda, Maryland**
**AIDS Clinical Trials Group (ACTG) Network**

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**National Institute of Allergy and Infectious Diseases**
**Division of AIDS (DAIDS)**
**Bethesda, Maryland**

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**IRB Initial Review Date: June 6, 2016**

# A PHASE 1, SINGLE DOSE STUDY OF THE SAFETY AND VIROLOGIC EFFECT OF AN HIV-1 SPECIFIC BROADLY NEUTRALIZING HUMAN MONOCLONAL ANTIBODY, VRC-HIVMAB080-00-AB (VRC01LS) OR VRC-HIVMAB075-00-AB (VRC07-523LS), ADMINISTERED INTRAVENOUSLY TO HIV-INFECTED ADULTS

SIGNATURE PAGE

I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable U.S. Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

Principal Investigator: _____
Print/Type

Signed: _____ Date: _____
Name/Title

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## ABBREVIATIONS

| Abbreviation | Term |
|---|---|
| ACTG | AIDS Clinical Trials Group |
| ADA | anti-drug antibody |
| ADL | activities of daily living |
| AE | adverse event |
| AIDS | Acquired Immunodeficiency Syndrome |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| AoU | Assessment of Understanding |
| ARV | antiretroviral |
| AST | aspartate aminotransferase |
| AUC | area under the curve |
| β-HCG | human chorionic gonadotropin |
| BMI | body mass index |
| CBC | complete blood count |
| CCR5 | CC family of chemokines, receptor type 5 |
| CL | clearance |
| CHO | Chinese Hamster Ovary |
| Cmax | maximum concentration |
| CRPMC | Clinical Research Products Management Center |
| CRS | cytokine release syndrome |
| cGMP | current Good Manufacturing Practice |
| DAERS | DAIDS Adverse Experience Reporting System |
| DAIDS | Division of AIDS |
| DAIDS MO | DAIDS Medical Officer |
| DAIDS PRO | DAIDS Protocol Registration Office |
| DHHS | Department of Health & Human Services |
| DNA | deoxyribonucleic acid |
| DSMB | Data and Safety Monitoring Board |
| EAE | expedited adverse event |
| EC | ethics committee |
| EC50 | half-maximal effective concentration |
| EDTA | Ethylenediaminetetraacetate |
| ELISA | enzyme-linked immunosorbent assay |
| Env | envelope |
| EOI | end of infusion |
| F | bioavailability |

| Abbreviation | Term |
|---|---|
| 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 |
| ISM | Independent Safety Monitor |
| IV | intravenous |
| kg | kilogram |
| L | liter |
| LIMS | Laboratory Information Management System |
| λz | terminal slope of concentration vs time profile |
| MAb | monoclonal antibody |
| mcg | microgram |
| mcL | microliter |
| mg | milligram |
| mL | milliliter |
| mM, mmol | millimole |
| MO | Medical Officer |
| MSD | Meso Scale Discovery |
| NIAID | National Institute of Allergy and Infectious Diseases |
| NIH | National Institutes of Health |
| NIH CC | National Institutes of Health Clinical Center |
| NHP | non-human primate |
| NVITAL | NIAID Vaccine Immune T-Cell and Antibody Laboratory |
| OHRP | Office for Human Research Protections |
| PBMC | peripheral blood mononuclear cells |
| PBS | phosphate buffered saline |
| PCR | polymerase chain reaction |
| PI | Principal Investigator |
| PK | pharmacokinetic |
| PSRT | Protocol Safety Review Team |
| Q | inter-compartmental clearance |

| Abbreviation | Term |
|---|---|
| QA | quality assurance |
| RE | regulatory entity |
| RSC | Regulatory Support Center |
| SAE | serious adverse event |
| SC | subcutaneous |
| SHIV | simian-human immunodeficiency virus |
| SSRI | selective serotonin reuptake inhibitor |
| 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 |
| VCMP | Vaccine Clinical Materials Program |
| Vd | volume of distribution |
| VRC | Vaccine Research Center |
| WBC | white blood cell |
| WT | Wild Type |

# PRÉCIS

| | |
|---|---|
| VRC 607/A5378: | A Phase 1, Single Dose Study of the Safety and Virologic Effect of an HIV-1 Specific Broadly Neutralizing Human Monoclonal Antibody, VRC-HIVMAB080-00-AB (VRC01LS) or VRC-HIVMAB075-00-AB (VRC07-523LS), Administered Intravenously to HIV-Infected Adults. |
| Study Design: | Open-label, single dose study to examine safety, tolerability, pharmacokinetics and virologic impact of VRC01LS or VRC07-523LS in HIV-infected viremic adults. |
| Study Hypotheses: | This is the first study of VRC01LS or VRC07-523LS in HIV-infected viremic adults. The primary hypothesis is that both VRC01LS and VRC07-523LS will be safe for intravenous administration to HIV-1-infected adults. The secondary hypothesis is that VRC01LS and VRC07-523LS will be detectable in human sera with a definable half-life. Part A (VRC01LS) of the study has completed enrollment. |
| Product Description: | VRC-HIVMAB080-00-AB (VRC01LS) and VRC-HIVMAB075-00-AB are human MAbs targeted to the $CD4^+$ binding site of HIV-1. Both MAbs are modifications of the VRC01 MAb (which has been shown to be safe and to have antiviral activity in human studies) with the addition of the "LS", a 2-amino acid mutation designed to improve the half-life of the antibody. There are no changes to the Fab binding sites. These MAbs were developed and manufactured by VRC/NIAID/NIH under cGMP at the VRC Vaccine Pilot Plant operated under contract by the Vaccine Clinical Materials Program (VCMP), Leidos Biomedical Research, Inc., Frederick, MD. Vials are provided at 100 mg/mL. |
| Participants: | HIV-1-infected viremic adults; 18-70 years of age. |
| Study Plan: | This study will assess VRC01LS or VRC07-523LS administered at 40 mg/kg IV in HIV-infected viremic participants. Participants will enroll in one of two parts: Part A (VRC01LS) and Part B (VRC07-523LS). Enrollment into Part A (VRC01LS) is complete. Part B enrollment will include 7 participants (up to 10 participants may be enrolled in the event that there are participants who do not complete the sampling schedule) who will receive VRC07-523LS. Safety lab samples, HIV viral load, $CD4^+$ count, PK samples, and blood samples for human anti-VRC01LS antibody (Part A) and human anti-VRC07-523LS antibody (Part B) detection will be drawn at baseline and intervals throughout the study. Participants will keep a daily diary of reactogenicity symptoms for 3 days after study product administration and will be queried at each study visit for adverse events. Participants in Part B will be strongly encouraged to initiate 3-drug ART (prescribed by their primary HIV clinician; not study-provided) any time after completing day 14 study evaluations.<br><br>Results from Part A and Part B may be analyzed, published, and presented separately since they involve two different MAbs. |

| VRC 607/A5378 Study Schema | | | |
|---|---|---|---|
| Parts | Participants | Product | Administration Schedule |
| | | | Day 0 |
| Part A (Enrollment complete) | 7 | VRC01LS | 40 mg/kg IV |
| Part B | 7 | VRC07-523LS | 40 mg/kg IV |
| Total* | 14 | | |
| *The expected enrollment is 14 participants (i.e., a minimum of 7 participants in each part). However, up to 20 participants (i.e., 10 participants in each part) may be enrolled in the event that there are participants who do not complete the sampling schedule, if additional PK evaluations are needed, or if additional participants are needed for safety evaluations. | | | |

Study Duration: Participants will be followed for 48 weeks after study product administration.

# 1. INTRODUCTION

The global incidence of new human immunodeficiency virus (HIV) infections 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, down from 2.9 million in 2005, with an estimated global total of 36.9 million people living with HIV. The reduction of HIV incidence is due to multiple factors that include prevention and treatment programs. The decrease in incidence is an encouraging trend, but the scope and cost of the epidemic remains of great global concern. The wider availability of antiretroviral (ARV) treatment, mother to child transmission prevention programs, and a diverse array of other prevention programs have all contributed to turning the tide of the epidemic [1]. Each effective form of prevention and treatment is a welcome public health measure.

The National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH) is committed to the development of safe, effective methods to prevent and treat HIV infection and AIDS worldwide. In this regard, the Vaccine Research Center (VRC), NIAID, Division of AIDS (DAIDS), NIAID, and AIDS Clinical Trials Group (ACTG) are collaborating to evaluate the potential clinical uses of HIV-specific broadly neutralizing human monoclonal antibodies (MAb) [2, 3, 4].

The VRC, NIAID, NIH developed VRC01LS and VRC07-523LS, highly potent and broadly neutralizing HIV-1 human MAbs targeted against the HIV-1 $CD4^+$ binding site [5]. The predecessor of VRC01LS and VRC07-523LS, VRC01, is in clinical trials under IND 113611 for prevention indication and under IND 126001 and IND 126664 for therapeutic indication. VRC01 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 [6]. The VRC01 sequence was modified by site-directed mutagenesis to increase its binding affinity for the neonatal Fc receptor (FcRn) and the resulting antibody was designated VRC01LS. 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 far outside of the antigen-binding site [7]. Other than the two amino acid difference, VRC01LS is identical to VRC01. VRC01LS has an extended half-life in both serum and mucosal tissue compared to VRC01, persists at higher concentrations in mucosal tissues, and has demonstrated improved protection against primate simian-human immunodeficiency virus (SHIV) infection [5]. VRC01LS is currently in clinical trials in HIV uninfected adults under IND 125494 for its HIV prevention indication. 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. Like VRC01LS, the LS mutation of VRC07-523LS was introduced by site-directed mutagenesis to increase the binding affinity for the neonatal Fc-receptor (FcRn), resulting in increased recirculation of functional IgG [5, 7], thus increasing plasma half-life.

In this study, VRC01LS or VRC07-523LS will be evaluated in HIV-1 infected participants for a potential treatment indication.

### 1.1 Rationale for the Study

The VRC considers the potential clinical uses for broadly neutralizing MAb in three broad areas: 1) prevention of transmission from HIV-1 infected mothers to newborn and breastfeeding infants, 2) prevention of HIV infection by sexual transmission, and 3) therapeutic application in HIV-1 infected individuals. This last application will be the focus of this study for a potential application of VRC01LS or VRC07-523LS in the management of HIV-1 infected people. The increased half-life and persistence of VRC01LS and VRC07-523LS at higher concentrations in mucosal tissues correlate with improved protection against SHIV infection *in vivo* in animal studies, suggesting a potential clinical application for the prevention or treatment of HIV-1 infection in humans. In this study, we will monitor the viral load and pharmacokinetics and pharmacodynamics of VRC01LS or VRC07-523LS among HIV-1 infected viremic adults to determine whether a therapeutic effect is present following the administration of one dose.

### 1.2 VRC01LS and VRC07-523LS Specific Research Laboratory Assessments

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

Laboratory assessments in the Phase 1 studies of the VRC01LS or the VRC07-523LS MAb include pharmacokinetics, assessment for the development of anti-VRC01LS or anti-VRC07-523LS antibody following exposure to the study products, and functional capacity (neutralization) of the MAbs following infusion.

Study product (VRC01LS or 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 MAb 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 (1 hour, 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. The 4-parameter logistic curve regression of a standard curve of the MAbs covering the range from 0.031 to 1.0 mcg/mL is utilized in this assay to quantitate the sample concentrations based upon the average of sample dilutions within the range of the assay.

Assessment for development of anti-VRC01LS or anti-VRC07-523LS antibodies in participants will be performed using the Meso Scale Discovery (MSD) platform based on electrochemiluminescence. The developed anti-drug antibody (ADA) assay uses the biotin-labeled VRC01LS or VRC07-523LS immobilized on a streptavidin-coated MSD plate as the capture molecule, and the SULFO-TAG labeled VRC01LS or VRC07-523LS as the reporter molecule. This assay is independent of the anti-VRC01LS or VRC07-523LS antibody isotype and permits the

detection of both high and low affinity antibodies. Additional testing may be conducted with VRC01-based assay if positive ADA is detected to VRC01LS or VRC07-523LS.

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, 9, 10].

As an exploratory evaluation, participants may be evaluated for their IgG1 allotypes to determine the potential for theoretical allotype-specific effects on the VRC01LS pharmacokinetics, such as reduced half-life or anti-drug antibody response [11, 12, 13]. Coded stored samples may be used for evaluation of the genetic sequence of the immunoglobulin heavy chain constant region allotype.

## 1.3 PREVIOUS HUMAN EXPERIENCE

VRC01LS and VRC07-523LS are very similar to their predecessor, VRC01. VRC01 was tested in two phase 1 clinical trials, VRC 601 (in HIV-1 infected adults) and VRC 602 (in healthy adults) (see Section 1.3.1) at the VRC. VRC01LS and VRC07-523LS are currently being evaluated in clinical trials in healthy adults at the VRC, NIH, Bethesda, MD. Initial safety data for VRC01LS (data from VRC 606) and VRC07-523LS (data from VRC 605) is summarized below

### 1.3.1 VRC01 Safety Data

Evaluations of the highly neutralizing antibody VRC01 as an investigational drug began in humans in September 2013. As of the beginning of January 2017, more than 840 adults have received 1 or more study product administrations of VRC01 in a dose range from 1 to 40 mg/kg through intravenous (IV) administration and at 5 mg/kg through subcutaneous (SC) administration. VRC01 has been tested in 27 HIV-infected adults in the VRC 601 study [14], in 29 and 84 healthy adults in VRC 602 [15] and HVTN 104 studies, respectively (IND 113611). Under IND 126001 in 2015, studies were initiated in HIV-1 infected adults to evaluate the safety and virological effect of VRC01 administration during acute HIV infection (RV398), during a brief analytical treatment interruption in chronically infected individuals (A5340), and the effect on the HIV reservoir (A5342).

Cumulatively across all studies to date (January 10, 2017), there have been no serious adverse events (SAEs) related to VRC01 that required expedited safety reporting to the US Food and Drug Administration (FDA) or other regulatory authorities, and no study safety pauses for adverse events (AEs). 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 Investigator's Brochure (IB) (Version 6.0, dated October 5, 2016). As of May 10, 2018, no SAEs related to VRC01 have been reported across all studies (communication from DAIDS).

SC administrations of VRC01 in adults have been associated with mild local reactions during product administration including some pruritus, redness, and swelling. Symptoms generally resolve within a few minutes to a few hours after completion of product administration. In adults, erythema/induration reactions were reported rarely; the largest observed diameter for erythema or induration events during infusions ranged up to about 9 cm.

In VRC 602, 2 out of 5 subjects who received a 5 mg/kg SC dose of VRC01 reported mild pain during product administration that resolved within 5-7 minutes. In VRC 606, 2 out of 2 subjects who received a 5 mg/kg SC dose of VRC01 reported moderate pain during product administration that resolved within 0-2 minutes. One (1) subject in VRC 601 (5 mg/kg SC) reported mild nausea during VRC01 SC administration.

Most subjects experienced mild systemic reactogenicity or none at all. The systemic symptoms most commonly reported were malaise/fatigue, myalgias, and headaches. Of the 3 subjects who reported severe systemic reactogenicity in the HVTN 104 study, 2 had concurrent viral infections, and 1 had malaise lasting 1 day.

Additional information on solicited reactogenicity in other studies can be found in the IB. Overall, the solicited local and systemic signs and symptoms following administration of VRC01 have generally been none to mild.

Adverse events attributed to VRC01 study product administration on the basis of temporal relationship that have not resulted in study product discontinuation include transient laboratory abnormalities (aspartate aminotransferase [AST], alanine aminotransferase [ALT], and creatinine elevation; decreased neutrophil count), diarrhea, herpes zoster, urticaria, dizziness, and pruritus at the administration site. Adverse events attributed to study product administration (VRC01 or placebo) on the basis of temporal relationship for which the schedule of study product administration was discontinued include one subject (placebo recipient) with mild chest discomfort and one subject with a mild generalized, pruritic, papular rash. The participant with rash had received a loading IV dose of VRC01 and 2 weeks later received another VRC01 dose by SC injection. Symptoms developed 3 days after the 2$^{nd}$ dose and had resolved by the next day. Both AEs resolved without clinical sequela. An HVTN 104 subject who experienced syncope a few hours after the IV infusion of VRC01 was also discontinued from the product administration schedule, although the event was assessed as unrelated.

In the P1112 study in infants, VRC01 has been very well tolerated when administered SC in either of the two single dose cohorts (Group 1 and Group 2) and in the monthly dose group (Group 3). There have been no systemic reactions to VRC01; local reactions (induration and/or erythema) have been mild and self-limiting.

Overall, VRC01 administration in the dose range from 1 to 40 mg/kg IV and at 5 mg/kg SC have been assessed as well-tolerated and safe for further evaluation [14, 15]. Refer to the current IB for a more updated information about the safety of VRC01.

### 1.3.2 VRC01LS Safety Data

Evaluation of VRC01LS began in the VRC 606 study in healthy adults in November 2015. The safety and PK data for the first 37 subjects who received administrations of VRC01LS were published in 2018 [16].

In summary, VRC01Ls administrations have been generally well tolerated when delivered IV or SC, and there were no SAEs or dose-limiting toxicity. Post-administration symptoms were mild or

moderate for local and systemic reactogenicity. Mild malaise and myalgia were the most common solicited AEs reported by 10 and 6 subjects, respectively. The most frequent local reaction was pain/tenderness at the injection site, reported by 14 subjects (2 for IV and 12 for SC administration) at a maximum severity being mild and moderate by 1 subject for SC product administration. 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 (Appendix IV). No systemic symptoms were reported during product administration.

Six (6) AEs were assessed as possibly related to VRC01LS administration and all were mild in severity. Two (2) reports of diarrhea, 1 in Group 1 (5 mg/kg, IV, subject 01606101) and 1 in Group 5 (5 mg/kg x 3 times, SC, subject 01606501), occurred on the day of VRC01LS administration and resolved the same day. One (1) Group 2 subject (5 mg/kg, SC, subject 01606201) experienced lightheadedness on the day following administration, and symptoms resolved within 24 hours. One (1) AE in Group 5 (5 mg/kg x 3 times, SC, subject 01606506) pertained to an injection site reaction with hyperpigmentation that resolved 14 days post administration. Two (2) AEs in Group 5 (5 mg/kg x 3 times, SC, subject 01606508) were due to elevated ALT levels (56 and 69 IU/L) on day 14 post injection and both resolved within 15 days after onset. No subject had a positive HIV enzyme immunoassay (EIA) response during the study.

As of January 17, 2018, 7 viremic participants were enrolled in Part A of VRC 607/A5378 and received one infusion of VRC01LS at 40 mg/kg IV as planned and are in follow-up. During VRC01LS administrations, no local or systemic reactogenicity was reported. All 7 participants reported maximal solicited local reactogenicity as “none” on a 3-day diary card. As to systemic solicited reactogenicity, one participant 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.

Refer to the IB for more details on the VRC01LS safety data.

### 1.3.3 VRC07-523LS Safety Data

As of January 15, 2018, the VRC 605 study is fully enrolled. Twenty-five (25) of 26 subjects received at least 1 dose of VRC07-523LS (12 SC and 25 IV administrations). One subject withdrew from the study prior to receiving the study product. There have been no SAEs and no study safety pauses for AEs. Overall, 15 of 25 subjects who received the product (60%) have had at least 1 AE with the maximum severity being Grade 1 for 7 subjects and Grade 2 for 6 subjects, Grade 3 for 1 subject and Grade 4 for 1 subject. The Grade 3 AE was for an elevated creatinine 56 days after the last product administration. This was most likely related to dehydration following exercise. The creatinine value was determined to be a Grade 3 based on the DAIDS Grading Table parameter of an increase of 1.5 to 2 times the baseline value, which was still well within the institutional normal range. The Grade 4 AE was for elevated liver enzymes likely related to starting a concomitant medication, fluoxetine, known to cause hepatoxicity, and not related to VRC07-523LS. VRC07-523LS administrations were discontinued for this subject due to the concomitant illness. While the

subject was being followed for safety, liver enzymes tests fluctuated again after starting citalopram, which reinforced that the event was most likely caused by an underlying sensitivity to selective serotonin reuptake inhibitor (SSRI) medications. This Grade 4 laboratory abnormality was not considered life-threatening as it was not clinically significant as there was no hospitalization, jaundice, coagulopathy, bleeding, or ascites. Six (6) mild or moderate AEs were assessed as related to study product including mild dizziness, 4 occasions of infusion reactions (1 mild and 3 moderate, reported for 2 subjects), and mild abdominal pain. All AEs assessed as related to the study product have resolved without residual effects.

Two (2) subjects developed infusion reactions shortly after IV product administration. Symptoms were typical of infusion reactions observed with other MAbs [17]. No atypical symptoms or delayed symptoms were seen. Specifically, one subject enrolled in the 40 mg/kg IV group experienced a moderate infusion reaction with chills, rigors, fever, myalgia, and headache beginning 15 minutes after completion of the infusion. The subject was treated with acetaminophen and ibuprofen. All symptoms resolved within 12 hours. Another subject in the 20 mg/kg IV group experienced 3 separate infusion reactions (n=2 moderate, n=1 mild) after each product infusion. The subject experienced nausea, chills, rigors, malaise, tachycardia, headache, myalgia, and arthralgia. Symptoms began 15 minutes to 1 hour after completion of each product administration and completely resolved within 12 hours. The subject was treated with acetaminophen and ibuprofen.

Overall, product administrations have been generally well tolerated with no unexpected reactions.

For solicited local reactions in the week after VRC07-523LS administrations, one of 17 subjects (5.9%) who received the product by IV administration reported mild bruising at the administration site, and 5 of 8 subjects (62.5%) who received the product SC reported mild pain/tenderness at the injection site [Investigator's Brochure, Version 4.0, dated February 26, 2018; VRC07-523LS VRC-HIVMAB075-00-AB CONFIDENTIAL 45].

For solicited systemic adverse events reported 3 days after product administration, 4 of 17 subjects (25%) receiving VRC07-523LS IV reported mild or moderate systemic reactogenicity symptoms. The reported symptoms were malaise (n=2 mild, n=1 moderate), myalgia (n=2 mild, n=1 moderate), mild headache (n=2), and moderate chills (n=2). Five (5) of 8 subjects (62.5%) receiving VRC07-523LS SC reported mild systemic reactogenicity symptoms: malaise (n=3), myalgia (n=2), headache (n=3), chills (n=1), nausea (n=1), and joint pain (n=2).

Refer to the IB for more details on the VRC07-523LS safety data.

### 1.3.4 Antiviral Effect of VRC01

Analysis of the VRC 601 viral load data obtained from 8 viremic adults showed that VRC01 has a statistically significant *in vivo* virological effect on HIV viral load when administered as a single 40 mg/kg IV dose. None of these adults were taking ARV when enrolled into the study and had not started ARV during the time period when the viral load data were collected. Six (6) of the 8 adult subjects had $\geq$1 $\log_{10}$ copies/mL decrease in viral load and 2 subjects had a viral load drop of 0.26 and 0.18 $\log_{10}$ copies/mL, respectively [15].

These data indicated the following for a single dose of VRC01 at 40 mg/kg IV:

- A statistically significant change from baseline viral load post-infusion days 5 to 16;
- The median time to reach ≥0.5 $\log_{10}$ decrease in viral load was 5 days; and,
- The median time to greatest decrease in viral load was 7 days.

A 0.5 $\log_{10}$ copies/mL or greater decrease in viral load is considered to be a positive response to ARV [18]. To have clinical benefit, such a change would need to be sustained. In VRC 601, subjects were administered only one dose of VRC01 at 40 mg/kg and, thus, a sustained effect on viral load was not expected.

### 1.4 Pharmacokinetic Parameters

Based on animal studies, VRC01LS has a 2.5- to 3-fold increase in half-life in macaques as compared to VRC01 [5]. The PK parameters of VRC01LS is currently under evaluation in VRC 606 in healthy individuals. In our interim, preliminary evaluation of the pharmacokinetics in VRC 606, VRC01LS appears to persist longer and at a higher serum concentration than VRC01 following infusion at comparable doses. Formal statistical and PK analysis is ongoing.

Based on the Gaudinski, et al. study of VRC01LS, the clearance for the 5-40 mg/kg dose range (n=16) was 36 ± 8 mL/d with an elimination half-life of 71 ± 18 days [16].

This trial will study VRC01LS and VRC07-523LS pharmacokinetics in HIV-1 infected adults.

## 2. STUDY PRODUCTS

The study products, VRC-HIVMAB080-00-AB (VRC01LS) and VRC-HIVMAB075-00-AB (VRC07-523LS), were produced under current Good Manufacturing Practice (cGMP) by VRC/NIAID/NIH at the VRC Vaccine Pilot Plant operated under contract by the Vaccine Clinical Materials Program (VCMP), Leidos Biomedical Research, Inc. (formerly SAIC-Frederick, Inc.), Frederick, MD. Specific manufacturing information is included on the study product vial labels and Certificates of Analysis, and can be found in the IBs. Quality Assurance (QA) lot release testing by the manufacturer and ongoing stability programs verify conformance to product specifications prior to use in clinical trials.

### 2.1 VRC-HIVMAB080-00-AB

VRC-HIVMAB080-00-AB (VRC01LS) is a broadly neutralizing human MAb targeted against the HIV-1 $CD4^+$ binding site. It was developed by VRC/NIAID/NIH.

VRC01 was modified by site-directed mutagenesis to increase its binding affinity for the neonatal Fc receptor (FcRn). The resulting antibody is designated VRC01LS. 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 far outside of the antigen-combining site [7]. The VRC01LS is an IgG1, and the glycosylation pattern is derived from its production in a Chinese Hamster Ovary (CHO) mammalian cell line.

The bulk lot of the drug substance was manufactured under cGMP using a stably transfected CHO cell line, purified, and the drug product vials were filled and labeled. Each product vial contains 6.25 mL volume at a concentration of 100 mg/mL VRC01LS in formulation buffer containing 25 mM sodium citrate, 50 mM sodium chloride, and 150 mM L-arginine hydrochloride at pH 5.8.

More details on the VRC-HIVMAB080-00-AB composition and manufacturing can be found in the IB.

## 2.2 VRC-HIVMAB075-00-AB

Like VRC01LS, VRC-HIVMAB075-00-AB (VRC07-523LS) is a broadly neutralizing human MAb targeted against the HIV-1 $CD4^+$ binding site. VRC07-523LS 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 2 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 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.

## 2.3 Preclinical Safety Studies

The *in vitro* preclinical safety studies performed to assess potential off target binding by VRC01LS and VRC07-523LS are summarized in Table 2.3-1. There was no unexpected off target binding.

| Table 2.3-1: *In Vitro* Preclinical Safety Studies with VRC01LS and VRC07-523LS | |
|---|---|
| Study Purpose | Study Outcome |
| Assessment of anti-phospholipid reactivity | VRC01LS does not react to phospholipids.<br>VRC07-523LS has slight reactivity to phospholipids. |
| Assessment of anti-nuclear antigen reactivity | VRC01LS does not react with nuclear antigens.<br>VRC07-523LS does react with a small subset of nuclear antigens. |
| Assessment of binding to a human epithelial cell line (HEp-2) by Immunohistochemistry | VRC01LS does not bind to HEp-2 cells.<br>VRC07-523LS has minimal reactivity with Hep-2 cells. |
| Assessment of potential "off target" binding in a human Tissue Cross-Reactivity study with VRC01LS and VRC07-523LS | VRC01LS variably stained cytoplasm and cytoplasmic granules in epithelial and/or decidual cells in several human tissues. The findings were judged of no toxicologic relevance for MAb [19, 20].<br>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. |

More information on these and other preclinical studies with VRC01LS and VRC07-523LS can be found in the IB.

## 2.4 NONHUMAN PRIMATE (NHP) STUDIES

Several non-GLP studies of VRC01LS and VRC07-523LS have been completed in NHP to assess for preclinical evidence of potential efficacy for prevention of HIV infection. Table 2.4-1 is a brief summary of the studies performed and supports the plan to evaluate up to 40 mg/kg dose administered IV as a dose range of potential interest for a preventive or therapeutic indication. More information on these studies can be found in the IB for both study products.

| Table 2.4-1: Pre-clinical Proof-of-concept Studies Performed with VRC01LS and VRC07-523LS in NHP | |
|---|---|
| Study Outcome | Study Purpose |
| Determine if VRC07-523LS could protect male Rhesus Macaques against SHIV infection compared to VRC01LS after IV administration of low sub-optimal protective dose (0.3 mg/kg) of MAb | 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* |
| Determine serum and rectal tissue concentrations in female rhesus macaques administered 10 mg/kg of VRC01 (WT) or VRC01LS IV | Introduction of the LS mutation increased the half-life of VRC01LS 2.5-fold and reduced clearance 3-fold compared to VRC01 (WT). VRC01LS remained detectable in rectal tissue for more than 70 days and persisted at significantly higher levels, while the VRC01 (WT) could not be measured after 28 days [5]. |
| Determine serum and mucosal sample concentrations in male and female cynomolgus macaques administered 10 mg/kg of VRC07-523LS IV or 10 mg/mL of VRC01LS IV | When administered IV at a single dose of 10 mg/mL in cynomolgus macaques, the half-life of VRC01LS was about 30 days, a 3-fold increase compared to VRC01 (WT). Increased levels of VRC01LS were noted in rectal tissue, rectal secretions, and vaginal tissue at 28 days post antibody infusion compared to VRC01 [5]. 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 serum and mucosal secretion concentrations in male and female rhesus macaques administered 10 mg/kg of VRC07-523LS SC or VRC01LS SC | When administered SC at a single dose of 10 mg/kg to rhesus macaques, the half-life of VRC01LS was about 28 days and VRC01LS was found in rectal, vaginal, and nasal secretions up to day 49 post administration (last day of testing). 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 VRC01LS or VRC07-523LS administered at 40 mg/kg IV to HIV-1 infected viremic adults.

## 3.2 SECONDARY OBJECTIVES

- To evaluate the pharmacokinetics of VRC01LS or VRC07-523LS at 40 mg/kg IV through the first 48 weeks post administration.
- To evaluate the effect on $CD4^+$ count and viral load through study week 48.
- To determine whether anti-drug antibody (ADA) to VRC01LS or VRC07-523LS can be detected post-administration.

## 3.3 EXPLORATORY OBJECTIVES

- To evaluate HIV-1 isolates throughout the study for a variety of genotypic and phenotypic parameters including sensitivity to VRC01LS or VRC07-523LS neutralization.

# 4. STUDY DESIGN

This is an open-label, single dose study to examine the safety, tolerability, pharmacokinetics, and virologic effect of the MAbs, VRC01LS or VRC07-523LS, in HIV-1 infected viremic adults conducted at the VRC and sites within the ACTG network. The hypothesis is that both VRC01LS and VRC07-523LS will be safe for administration to HIV-1 infected adults by the IV route. The secondary hypothesis is that VRC01LS and VRC07-523LS will be detectable in human sera with a definable half-life.

The study schema is shown in Table 4-1.

Table 4-1. VRC 607/A5378 Study Schema

| Parts | Participants | Product | Administration Schedule |
|---|---|---|---|
| | | | Day 0 |
| Part A (Enrollment Complete) | 7 | VRC01LS | 40 mg/kg IV |
| Part B | 7 | VRC07-523LS | 40 mg/kg IV |
| Total* | 14 | | |

*The expected enrollment is 14 participants (i.e., a minimum of 7 participants in each part). However, up to 20 participants (i.e., 10 participants in each part) may be enrolled in the event that there are participants who do not complete the sampling schedule, if additional PK evaluations are needed, or if additional participants are needed for safety evaluations.

Enrollment into Part A (VRC01LS) is complete. Participants will be enrolled into Part B (VRC07-523LS). Blood and urine samples for safety laboratory, and PK evaluations will be collected from all participants at specified time points per the Schedule of Evaluations (Appendix III). Participants will keep a daily diary of solicited systemic symptoms for 3 days after product administration. Participants will be strongly encouraged to initiate 3-drug antiretroviral therapy (ART), that is prescribed by their primary HIV clinician and not study-provided, any time after completing day 14 study evaluations. PK-enhancing agents will not be counted as part of the 3-drug ART regimen.

## 4.1 STUDY POPULATION

All inclusion and exclusion criteria must be met for eligibility.

### 4.1.1 Inclusion Criteria

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

1. Able and willing to complete the informed consent process.
2. 18-70 years old
3. Available for clinic visits for 48 weeks after study product administration.
4. HIV-1 infected and clinically stable.
   [Note: Documented HIV-1 infection by HIV enzyme immunoassay (EIA) performed by a CLIA certified outside lab within 28 days of enrollment is acceptable.]
5. At least one plasma viral load ≥500 copies/mL within 28 days of enrollment. A plasma viral load within 28 days and closest to the day of enrollment, that is detectable but not greater than 100,000 copies/mL.
   [Note: outside laboratory results will be acceptable].
6. A $CD4^+$ count ≥350 cells/mcL on 2 of 3 consecutive testing occasions (or on 2 of 2 sequential tests) within 28 days prior to enrollment.
   [Note: outside laboratory results will be acceptable].
7. In general good health as assessed by a study clinician and under the care of a primary health care provider for medical management of HIV infection while participating in the study. Willing to give consent to contact and send laboratory results to the participant's primary health provider.
8. Willing to have blood samples collected, stored indefinitely, and used for various research purposes.
9. Able to provide proof of identity to the satisfaction of the study clinician completing the enrollment process.
10. Screening laboratory values within 28 days prior to enrollment must meet the following criteria:
    - Absolute neutrophil count ≥800/mcL

- Platelets ≥100,000/mcL
- Hemoglobin ≥10.0 g/dL
- Creatinine ≤1.31 mg/dL
- ALT ≤2.5 x ULN
- Negative Hepatitis B Surface Antigen (HBsAg)
- Undetectable Hepatitis C Viral Load (HCV RNA)

[Note: Documented negative HBsAg and HCV RNA performed by an outside CLIA certified lab within 28 days of enrollment are acceptable.]

*Female-Specific Criteria:*

11. If a woman is sexually active with a male partner and has no history of hysterectomy, tubal ligation, or menopause, she must agree to use either a prescription birth control method or a barrier birth control method from the time of study enrollment until the last study visit, or have a monogamous partner who has had a vasectomy.
12. 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 participant will be excluded if one or more of the following conditions apply*:

1. Previous receipt of humanized or human monoclonal antibody whether licensed or investigational.
2. Prior use of antiretroviral therapy.
3. Ongoing AIDS-related opportunistic infection (including oral thrush).
4. Active drug or alcohol use or dependence in the opinion of the site investigator that would interfere with adherence to study requirements.
5. Any history of a severe allergic reaction, including generalized urticaria, angioedema or anaphylaxis prior to enrollment, that has a reasonable risk of recurrence during the study.
6. Physical finding on examination considered clinically significant.
7. Hypertension that is not well controlled.
8. Weight >115 kg (253 pounds).
9. Breast-feeding.
10. Receipt of any investigational study product within 28 days prior to enrollment.
11. Any other chronic or clinically significant medical condition that in the opinion of the investigator would jeopardize the safety or rights of the volunteer.

## 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 participant will comply with the NIH Clinical Center Guidelines, which is available on the NIH intranet at: http://cc-internal.cc.nih.gov/policies/PDF/M95-9.pdf.

All participants will be counseled to continue follow up with their primary HIV care provider throughout the duration of the study and to follow the DHHS guidelines to initiate ARVs for all HIV-infected individuals, regardless of $CD4^+$ count. The study team will ensure that all participants have a primary health provider for medical management of HIV infection while participating in the study. Participants will be informed about the risks of not starting on ARV.

- In Part A, participants will be encouraged to start ARVs in the following situations specifically (with documentation): prior to enrollment into the study; at the time of any increase in viral load; when the $CD4^+$ count drops by 30%; when the $CD4^+$ cell count drops below 200 cells/$mm^3$; and should a female participant become pregnant during the study.
- In Part B, initiation of 3-drug ART (prescribed by primary HIV clinician; not study-provided) will be strongly encouraged after participants complete day 14 study evaluations. PK-enhancing agents will not be counted as part of the 3-drug ART regimen.

Participants who are viremic on ARVs will be encouraged to talk to their primary care provider about their ARV regimen, per DHHS guidelines [21].

Participants who receive the study product will continue to be followed for safety purposes according to the study schedule of evaluations. Participants will not be discontinued or replaced in the study for initiating or changing ARVs. They will continue to be followed for safety purposes according to the study schedule of evaluations. ARV regimen changes will be documented in the participant's record. Additionally, PK assay for ARVs will be performed in Part B, if needed, to evaluate for the presence of ART and the period before and during viral rebound in participants who initiate ART. Data will be analyzed according to the Statistical Analysis plan in Section 6.4.

In Part B, a participant who does not complete all of the required visit through day 14 will be replaced (up to a total of 10 participants enrolled).

### 4.2.1 Screening

Screening for Part A: (This part of the study has completed enrollment.)

The screening protocol, VRC 500 (NIH 11-I-0164), will be used at the sites to screen for potential participants. Participants 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. Samples of PBMCs, plasma and serum will also be collected. Informed consent documents will be reviewed. Counseling related to pregnancy prevention (including

potential risk of study product) will be performed at screening and subsequently as noted in the Schedule of Evaluations in Appendix III. Screening records will be kept documenting the reason why an individual was screened but not enrolled into the clinical trial.

Screening for Part B:

Screening evaluations to determine eligibility must be completed within 28 days prior to study enrollment unless otherwise specified. Screening evaluations, as noted in the Schedule of Evaluations in Appendix III, must occur prior to the participant starting any study products, treatments, or interventions.

### 4.2.2 Enrollment, Study Days and Visit Numbers

In this study, enrollment is defined as the day of assignment of a study identification number in the clinical database. A clinician will discuss the timing of the study product administration and blood sample collection before completing an enrollment to help ensure that the participant can comply with the projected schedule. Positive prevention counseling will be performed at enrollment and subsequently as noted in the Schedule of Evaluations. An Assessment of Understanding (AoU) will be completed in association with screening into VRC 607/A5378. The schedule will not require administration in an inpatient unit or an overnight stay but inpatient administration is an option to facilitate collection of timed research samples.

Day 0 is defined as the day of study product administration. Day 0 may occur on the same day as enrollment, or up to 4 weeks (28 days) after enrollment in Part A or up to 10 days after enrollment in Part B. This period may be increased with approval from the protocol team (contact the protocol team at actg.teama5378@fstrf.org).

For calculating elapsed days, each subsequent calendar date is labeled by the next sequential "Study Day" as shown in the Schedule of Evaluations in Appendix III. Because there may be more than 1 research sampling timepoint of interest per study day, each sample collection timepoint has its own "Visit Number." For this reason, there may be more than one visit number recorded on the same calendar date.

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

### 4.2.3 Administration of Study Product

All study product administrations will be completed according to the study schema. For women of childbearing potential, study product administration may not proceed unless a negative pregnancy test has been obtained on the day of enrollment and on the day of study product administration (Day 0). Prior to 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.

The IV access will be placed in an arm in an aseptic manner. A different site will 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. Study product will be administered with approximately 100 mL normal saline IV with a target of about 30 minutes. Infusions lasting longer than 30 minutes are allowed. If there is evidence of intolerance by the participant, the infusion rate will be slowed or stopped.

All participants will be observed for at least 30 minutes following product administration.

### 4.2.4 Solicited Adverse Events and Clinical Follow-up

Participants will be given a "Diary Card" to use as a memory aid for solicited adverse events and on which to record temperature and systemic symptoms daily for 3 days after study product administration. Participants will be trained to use a secure electronic database but may complete the paper "diary", if preferred. When the 3-day diary card parameters are recorded directly by the participant through a password-protected secure database, the participant'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 diary card data, or if a participant uses a paper diary card, clinicians may follow up with additional phone calls during the reactogenicity period, as needed. The written (paper) diary may be used as a source document. When neither a written nor electronic diary card is available from the participant, the study clinician will note the source of reactogenicity information recorded in the study database.

After receipt of study product solicited systemic parameters occurring within 3 days include: fever, unusually tired/feeling unwell, muscle aches, headache, chills, nausea, and joint pain. Participants will record highest measured temperature daily. Reactogenicity data will be reviewed for accuracy and completeness at follow-up visits and recorded without an attribution assessment. Clinicians will follow up with participants and collect resolution information for any reactogenicity symptoms that are not resolved within 3 days.

Local reactogenicity parameters will include pain/tenderness, swelling, redness, bruising, and pruritus (itchiness) at the product administration site. Clinician assessment of the IV administration site will be conducted on day of study product administration and during the scheduled follow-up timepoints after product administration.

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). 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.

### 4.2.5 Pharmacokinetics Procedures

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

### 4.2.6 Schedule of Evaluations

Refer to the table in Appendix III for details on the Schedule of Evaluations and the windows permitted for completion of each visit. After enrollment, deviations from the visit windows are discouraged and will be recorded as protocol deviations, but will be permitted at the discretion of the PI (or designee).

Additional visits and diagnostic tests may be scheduled during the study if needed to assess participant safety or for sample collection for immunological testing.

Any evaluation for an adverse event or possible exacerbation of a pre-existing condition may be evaluated at study team discretion as a "protocol related" evaluation (contact the protocol team at actg.teama5378@fstrf.org).

In the event that Grade 2 or higher proteinuria is detected, a nephrology consultation will be arranged, as well as any other clinically necessary investigations.

### 4.2.7 Monitoring HIV Infection Status

HIV infection status will be monitored at specified intervals by $CD4^+/CD8^+$ T cell count and HIV-1 RNA PCR for viral load. $CD4^+$ counts are known to have diurnal variation; therefore, participants will be encouraged to return for appointments that include $CD4^+$ count at approximately the same time (e.g., morning or afternoon), whenever possible.

If the $CD4^+$ count decreases to less than 200 cells/mcl, the participant will be promptly informed and strongly urged to seek evaluation and advice from their primary HIV care provider. Documentation of ARV counseling session performed by study staff to review current DHHS guidelines for ARV therapy will be included in the research record.

### 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 adverse event that requires expedited reporting or the development of a new chronic condition requiring ongoing medical management will be recorded in the database. Otherwise, concomitant medications taken throughout the study will be recorded in the participant's chart as needed for general medical records, but will not be recorded in the study database. In Part B, participants will be strongly encouraged to initiate 3-drug ART (prescribed by their primary HIV clinician; not study-provided) any time after completing day 14 study evaluations. PK-enhancing agents will not be counted as part of the 3-drug ART regimen. The ART therapy will be documented as concomitant medications and any changes in the ARV regimen will be recorded in the database.

## 4.3 Discontinuation of Study Participation Following Product Administration

Under certain circumstances, a participant may be terminated from participating in the study or may choose to withdraw participation. A participant may be terminated from participating in the study for any of the following reasons:

- Repeatedly non-compliant (missing visits or not following study procedures)
- Develops a serious illness requiring ongoing medical care
- Enrolls in another research study while on this study
- Pregnancy
- Study is stopped or canceled

Participants who received study product will be asked to continue follow-up visits for safety monitoring purposes according to the protocol (Schedule of Evaluations, Appendix III), but collection of samples that are for research purposes only will be discontinued. Women who become pregnant will be asked to continue follow-up for safety monitoring (in which case we do not continue research blood draws) and to report the outcome of the pregnancy to the study team. The study team will notify the Antiretroviral Pregnancy Registry (http://www.apregistry.com; Telephone: 800-258-4263; Fax: 800-800-1052) of any pregnancies that occur after receiving study product for any participant still on the study.

### 4.4 Protocol Criteria for Pausing the Study and Resuming the Study

Administration of the study products and new enrollments will be paused by the protocol team according to the criteria noted below. In the event of a pause, the IND Sponsor Medical Officer (MO) and Independent Safety Monitor (ISM) will be promptly notified. Refer to Section 5.3.2, for definitions of "related" and "not related" to study product when using these study pause criteria. Pause criteria are as follows:

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

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

### 4.5 Plan for Review of Pauses and Resuming Rules

Administration of the study product and enrollments would resume only if review of the adverse events that caused the pause resulted 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 MO, with participation by the protocol team, will conduct the review and consult with the FDA to make the decision to resume, amend, or close the study, and notify the IRB accordingly.

Pauses for related Grade 3 Events: The IND Sponsor MO, in consultation with the protocol team, will conduct the review and make the decision to resume, amend, or close the study for the Grade 3 that meet the criteria for pausing the study. As part of the pause review, the reviewers will also advise on whether the study needs to be paused again for any subsequent events of the same type. The FDA and the IRB will be notified of grade 3 pause reviews and the IND sponsor 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 participant, 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. In the event of proteinuria Grade 2 or higher, a nephrology consultation will be arranged, as well as other clinically necessary investigations.

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 from:

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

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 (or 8 weeks) after study product administration.

## 5.2 SERIOUS ADVERSE EVENTS (SAE)

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 adverse event that at occurrence represents an immediate risk of death to the participant. 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 an SAE. In Section 5.3 the term "Expedited Adverse Event" (EAE) encompasses the events that would be considered an SAE by the 21 CFR 312.32 definition.

## 5.3 ADVERSE EVENT REPORTING TO THE IND SPONSOR

### 5.3.1 Expedited Adverse Event (EAE) Reporting Criteria

Requirements, definitions and methods for expedited reporting of AEs are outlined in Version 2.0 (January 2010) of the *Manual for Expedited Reporting of Adverse Events to DAIDS* (DAIDS EAE

Manual), which is available on the Regulatory Support Center (RSC) website at http://rsc.tech-res.com/clinical-research-sites/safety-reporting. The SAE Reporting Category will be used for this study.

The internet-based DAIDS Adverse Experience Reporting System (DAERS) will be used for expedited AE reporting to DAIDS. In the event of system outages or technical difficulties, expedited AE reports may be submitted via the DAIDS EAE Form. This form is available on the DAIDS RSC website at http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids/paper-eae-reporting. For questions about DAERS, please contact NIAID CRMS Support at CRMSSupport@niaid.nih.gov or from within the DAERS application itself. For questions about expedited reporting, please contact the DAIDS RSC Safety Office at (DAIDSRSCSafetyOffice@tech-res.com).

The study products for which expedited reporting is required is as follows:

- VRC-HIVMAB080-00-AB (VRC01LS MAb)
- VRC-HIVMAB075-00-AB (VRC07-523LS MAb)

The NIAID/DAIDS will report all unexpected SAEs related to the study products observed in this clinical trial to the FDA in accordance with 21 CFR 312.32 (IND Safety Reports).

While the participant is in the study reporting period, as defined in Section 5.1, the SAE Reporting Category will be used.

The EAE Manual should be consulted for further details. Also, ensure that any protocol-specific reporting requirements are met.

An EAE report form will be completed and reported to DAIDS within 3 days of investigator awareness, regardless of relationship to study product.

The SAE criteria are as follows:

- Results in death
- Is life-threatening[1]
- Requires (unplanned) inpatient hospitalization or prolongation of hospitalization[2]
- Results in persistent or significant disabilities/incapacity.
- Is a congenital anomaly/birth defect[3]
- Is an important medical event (may jeopardize the patient or may require intervention to prevent one of the outcomes above

Footnotes:

[1] "Life-threatening" refers to an event in which the patient was at immediate risk of death at the time of the event. It does NOT refer to an event that hypothetically might have caused death if it were more severe.

[2] Per ICH SAE definition, hospitalization is NOT an adverse event (AE), but is an outcome of the event. DO NOT REPORT: Any admission unrelated to an AE (e.g., for labor/delivery, cosmetic surgery, administrative or social admission for temporary placement for lack of a place to sleep); protocol-specified admission (e.g., for a procedure required by protocol); admission for diagnosis or therapy of a condition that existed before receipt of study product(s) and has not increased in severity or frequency as judged by the clinical investigator. (NOTE: A new AIDS-defining

event in a subject already known to be HIV-infected would be considered an increase in severity of a pre-existing condition [HIV infection] and would be reportable.)

[3] Clinically insignificant physical findings at births including those regarded as normal variants do NOT meet reporting criteria. If a clinically significant anomaly is reported, all findings (including those of no individual significance) should be included in the same report. For example, do NOT report an isolated finding of polydactyly (extra fingers or toes) or Mongolian spot in an infant. But if either finding occurred with a major cardiac defect, report all findings in the SAE Report.

### 5.3.2 Attribution Categories

Attribution categories used (i.e., terms used for assessment of relationship of AE to study product) for this study are consistent with those described in the DAIDS EAE Manual, Version 2.0 (January 2010), as follows:

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

If circumstances arise where other attribution categories are used in describing an adverse event, the attribution terms "Definitely", "Probably" and "Possibly" related will be mapped to the "Related" category while the terms "Unlikely", "Probably Not Related" and "Not Related" will be mapped to the "Not Related" category under EAE Manual, Version 2.0.

## 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 participant population being studied; and
- Related to participation in the research; and
- Suggests that the research places participants 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 adverse event, but which may, in the opinion of the investigator, involve risk to the participant, 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:

- 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 an SAE or compromises the safety, integrity of the data, welfare, or rights of participants 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 participants. 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 IRB

Sites under the oversight of the NIAID IRB will report the following to the IRB within 7 calendar days of investigator awareness:

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

The following waiver applies to reporting anticipated protocol deviations and expected UPnonAEs: Anticipated deviations in the conduct of the protocol will not be reported to the IRB unless they occur at a rate greater than anticipated by the study team. Expected adverse events 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.

For Part B, ACTG sites under the oversight of a local IRB will follow their local IRB guidelines for expedited reporting.

### 5.4.5 Annual Reporting to the IRB

Sites under the oversight of the NIAID IRB will report the following to the IRB in a summary at the time of Continuing Review:

- Serious and non-serious UP
- 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

For Part B, ACTG sites under the oversight of a local IRB will follow their local IRB guidelines for annual reporting.

## 6. STATISTICAL CONSIDERATIONS

### 6.1 OVERVIEW

A phase 1, single dose study of the safety and virologic effect of HIV-1 specific broadly neutralizing human monoclonal antibodies, VRC-HIVMAB080-00-AB (VRC01LS) or VRC-HIVMAB075-00-AB (VRC07-523LS), administered intravenously to HIV-infected adults. In Part B, as participants will be strongly encouraged and some may initiate 3-drug ART (prescribed by their primary HIV clinician; not study-provided; PK-enhancing agents not counted in the ART regimen) after completing day 14 study evaluations, all analysis will be done separating the two periods of time (off concomitant ART and on concomitant ART).

Results from Part A and Part B may be analyzed, published, and presented separately since they involve two different MAbs.

### 6.2 OBJECTIVES

The primary objective is to evaluate the safety and tolerability of either VRC01LS or VRC07-523LS administered at 40 mg/kg IV to HIV-1 infected viremic adults. Secondary objectives include evaluation of the pharmacokinetics and the effects on $CD4^+$ and viral load through the first 48 weeks post administration of the study products, as well as the presence of anti-drug antibody response. Exploratory objectives include evaluating HIV-1 isolates throughout the study for a variety of genotypic and phenotypic parameters including sensitivity to VRC01LS or VRC07-523LS neutralization.

## 6.3 SIZE AND ACCRUAL

Recruitment will target about 14 HIV-1 infected viremic adults of age 18-70, 7 participants enrolled in each part (Part A and Part B). The permitted accrual is 20 participants (or up to 10 participants in each part) to allow for additional enrollments in the event that some participants do not complete the sampling schedule, if additional PK evaluations are needed, or if additional participants are needed for safety evaluations.

A participant in Part B who does not complete all of the required visits through day 14 will be replaced up to a maximum of 10 participants enrolled.

### 6.3.1 Sample Size Considerations

This study is primarily descriptive. For safety analysis, the goal is to identify safety concerns associated with the products.

The ability of the study to identify SAEs will be expressed in terms of the probability of observing a certain number of serious adverse events. Useful values are the minimum true rate such that the probability of observing at least one event is at least 90%, and the maximum true rate such that the probability of not observing any event is at least 90%. With n=7 participants in an arm, there is over 90% chance to observe at least one SAE if the true rate is at least 0.281 and over 90% chance to observe no SAE if the true rate is no more than 0.014.

Probabilities of observing zero or more than 1 serious adverse event are presented in Table 6.3-1 for a range of possible true event rates. These calculations provide a more complete picture of the sensitivity of this study design to identify potential safety problems with the product.

Table 6.3-1: Probability of Event for Different Scenarios (n=7)

| True event rate | Pr (observing zero events) | Pr (observing more than one event) |
|---|---|---|
| 0.005 | 0.966 | 0.001 |
| 0.010 | 0.932 | 0.002 |
| 0.020 | 0.868 | 0.008 |
| 0.035 | 0.779 | 0.023 |
| 0.050 | 0.698 | 0.044 |
| 0.100 | 0.478 | 0.15 |
| 0.150 | 0.321 | 0.283 |
| 0.200 | 0.21 | 0.423 |
| 0.300 | 0.082 | 0.671 |

Table 6.3-2 gives the upper and lower bounds for 95% exact binomial confidence intervals of the true SAE rate at all possible numbers of events. If none of the 7 participants experience serious adverse events, the 95% exact 2-sided upper confidence bound for the SAE rate is 0.41.

Table 6.3-2: 95% Confidence Intervals for the True Rate at Possible Observed Number of Events (n=7)

| # of observed events | 95% Confidence Interval | |
|---|---|---|
| | Lower Bound | Upper Bound |
| 0 | 0 | 0.410 |
| 1 | 0.004 | 0.579 |
| 2 | 0.037 | 0.710 |
| 3 | 0.099 | 0.816 |
| 4 | 0.184 | 0.901 |
| 5 | 0.290 | 0.963 |

Tables 6.3-1 and 6.3-2 apply to the secondary binary 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.

### 6.4.3 Safety Analysis

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

Solicited Adverse Events:

Solicited AE data will be collected after each study product administration. The number and percentage of participants experiencing each type of solicited sign or symptom will be tabulated by severity. For a given sign or symptom, each participant's solicited AEs will be counted once under the maximum severity for all assessments.

Unsolicited Adverse Events:

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 participant [17]. VRC 607/A5378 is the first trial of VRC01LS or VRC07-523LS in HIV-1 viremic adults. The tolerability evaluation will be mostly descriptive by nature and consist of solicited AEs that occur during the 3 days following study product administration and reasons for any withdrawal or discontinuation based upon participant discomfort. This early assessment of tolerability of VRC01LS or VRC07-523LS will inform which parameters should be solicited or routinely assessed to further characterize the tolerability profile in a larger number of participants.

### 6.4.5 Analysis of effect on $CD4^+$ and HIV Viral load

The positive response rate and the magnitude of $CD4^+$ response will be evaluated through 48 weeks post product administration. The profile of HIV viral load will be evaluated both numerically and graphically.

In Part B, as participants will be strongly encouraged and some may initiate 3-drug ART (prescribed by their primary HIV clinician; not study-provided; PK-enhancing agents not counted in the ART regimen) after completing day 14 study evaluations, all analysis will be done separating the two periods of time (off concomitant ART and on concomitant ART).

### 6.4.6 Pharmacokinetics Analysis

Blood samples for PK evaluations will be collected at time points defined in the Schedule of Evaluations (Appendix III).

Individual Participant Pharmacokinetic Analysis: A non-compartmental PK analysis will be performed using Phoenix (Centara) or a similar program on the VRC01LS or VRC07-523LS concentration data generated from each participant. Calculated PK parameters will include: area-under-the-curve (AUC), maximum concentration ($C_{max}$), clearance (CL), volume of distribution (Vdz), terminal elimination rate constant ($\lambda_z$), and the terminal half-life ($T_{1/2}$). $C_{max}$ will be taken directly from the observed concentration-time data. The terminal slope, $\lambda_z$, will be determined from the log-linear portion of the curve and the terminal $T_{1/2}$ 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 336 days or the

earlier if earlier samples are below the quantitative limit or the participant does not complete the final PK sample collections. If the final sample, $C_{last}$, has measurable VRC01LS or VRC07-523LS concentrations, the remaining AUC after the final concentration ($AUC_{Clast-inf}$) will be estimated as $C_{last}/\lambda_z$. Additional compartmental analysis will be performed as warranted by the data.

Population Pharmacokinetic Analyses: Population PK analyses will be performed on the VRC01LS and the VRC07523LS PK data following IV administration to determine compartmental PK parameters with the program NONMEM. One, two, and three 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), and CL. Given the small participant numbers, the population PK analysis will not include an exploratory covariate analysis to assess clinical factors as fixed effects associated with VRC01LS and VRC07-523LS PK parameters. 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 visual posterior predictive check. VRC01LS and VRC07-523LS dosing strategies and their ability to achieve and maintain target study product concentrations will be performed using the final population PK model and Monte Carlo simulations with at least 5000 replicates.

In Part B, as participants will be strongly encouraged and some may initiate 3-drug ART (prescribed by their primary HIV clinician; not study-provided; PK-enhancing agents not counted in the ART regimen) after completing day 14 study evaluations, all PK analysis will be done separating the two periods of time (off concomitant ART and on concomitant ART). Additionally, PK analysis for ARVs will be performed in Part B, if needed, to evaluate for the presence of ART and the period before and during viral rebound in participants who initiate ART.

### 6.4.7 Interim Analyses

Preliminary analyses of pharmacokinetics may be done once participants complete Visit 21 (week 24). This preliminary information will be used for subsequent studies that may begin while VRC 607/A5378 is still in progress.

## 7. PHARMACY PROCEDURES

Refer to the IB for further information about the investigational study products.

### 7.1 Study Products and Administration Regimen

VRCHIVMAB080-00-AB (VRC01LS) and VRC-HIVMAB075-00-AB (VRC07-523LS) are supplied at a concentration of 100 (± 10) mg/mL an isotonic and sterile solution; two fill volumes are available, 2.25 ± 0.1 mL in a 3mL 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 for VRC01LS is composed of 25 mM sodium citrate, 50 mM sodium chloride, and 150 mM L-arginine hydrochloride at pH 5.8. The

formulation buffer for VRC07-523LS 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.

VRC01LS and VRC07-523LS are highly concentrated protein solutions 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 2°C to 8°C.

For Part A, VRC01LS will be administered as 40 mg/kg IV once on D0.

For Part B, VRC07-523LS will be administered as 40 mg/kg IV once on D0.

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 2 mL or 6 mL can be withdrawn from a vial. In this trial, dose is limited or established based on participant weight.

Preparation of VRC01LS or VRC07-523LS will require a 100 mL bag of 0.9% sodium chloride for injection, 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 VRC01LS or VRC07-523LS is added and this is acceptable in the context of the instructions below.

## 7.2 Vialed Study Product Storage

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

Following thaw, vials of VRC01LS may be stored for up to 24 hours at controlled room temperature (maximum 27°C) and/or up to 4 weeks at 2°C to 8°C. Following thaw, vials of VRC07-523LS may be stored for up to 24 hours at controlled room temperature (maximum 27°C) and or up to 2 weeks at 2°C to 8°C. Products may not be stored in direct sunlight. If stored at 2°C to 8°C, vials must be equilibrated to controlled room temperature (maximum 27°C) for a minimum of 30 minutes and may be held at room temperature for up to 8 hours prior to product preparation.

### 7.2.1 Temperature Excursions

The site pharmacist must promptly report any storage temperature excursions outside of the normal allowance to the IND sponsor (see 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.

## 7.3 Preparation of Study Products for Administration

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

The following instructions apply to thawing VRC01LS and VRC07-523LS:

1. Thaw vials for a minimum of 1 hour at controlled room temperature (maximum 27°C) after removing from freezer.
2. Keep the material at controlled room temperature (maximum 27°C) during the preparation period, 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 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 IV administration. Refrigerated product must be equilibrated at controlled room temperature (maximum 27°C) 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.

### 7.3.1 VRC-HIVMAB080-00-AB or VRC-HIVMAB075-00-AB: Preparation for IV Administration

For each IV infusion order, the participant's weight, dosage, and group will be included in the pharmacy order. The weight measured within 10 days prior to the scheduled study product administration (Day 0) can be used. 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 milligrams needed to a 100 mL bag of normal saline using good pharmacy practices to maintain sterility. Prior to preparation for administration, the vials should be gently swirled for 30 seconds to avoid foaming. DO NOT SHAKE THE VIAL. Typically, 50 to 100 mL of additional volume may be added to 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 for additional volume. Refer to the Manual of Procedures for Part B for alternative preparation instructions if 100 mL bags of normal saline are not available.

After preparation in IV bags, the prepared product may be stored at 2°C to 8°C up to 24 hours or at room temperature (maximum 30°C) for a maximum of 8 hours total including the infusion time, out of direct sunlight. If stored at 2°C to 8°C, prepared product must be equilibrated to room

temperature (maximum 30°C) for a minimum of 30 minutes prior to product administration. Prior to IV administration, the nurse responsible for administration and another clinician will each check the bag label and confirm that the identifier is correct and that the correct total mg to be administered is shown based on the participant's current weight.

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

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

### 7.4 Labeling of Study Products

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

The prepared IV product label shall contain:

- Participant identifier
- Participant weight (kg)
- Dose of VRC01LS or VRC07-523LS (40 mg/kg) and total amount (mg) added to the NS bag
- Final volume of the IV product
- For IV administration
- Lot number
- Do not infuse after date and time:
    - 24 hours, if stored at 2°C to 8°C
    - 8 hours, if stored at controlled room temperature (not to exceed 27°C)

### 7.5 Study Product Distribution/Accountability

The VRC will follow the NIH CC pharmacy SOP for distribution and accountability of the study product.

For the ACTG sites, VRC07-523LS will be available through the NIAID Clinical Research Products Management Center (CRPMC). The site pharmacist should obtain the study product for this protocol by following the instructions in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* manual.

Due to the small sample size, study product will be shipped to each site as participants are enrolled. The site staff should coordinate with their respective site pharmacy to inform the pharmacist when a

participant is being enrolled so an order for study product can be placed with the CRPMC. Study product should be available on site one day prior to the scheduled infusion (D0). Refer to the MOP for detailed study product ordering instructions.

The site pharmacist is required to maintain complete records of all study products received from the NIAID CRPMC and subsequently dispensed.

### 7.6 Study Product Disposition

At VRC, the empty vials and unused portions of a vial will be discarded as per NIH CC pharmacy SOP.

At ACTG sites, all unused study products at US Clinical Research Sites must be returned to the NIAID CRPMC (or as otherwise directed by the sponsor) after the study is completed or terminated. The procedures to be followed are in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* manual.

## 8. HUMAN SUBJECT PROTECTIONS AND ETHICAL OBLIGATIONS

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

### 8.1 Informed Consent

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

Before an individual's participation in the study, it is the investigator's responsibility to obtain written ICF from the participant, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific procedures are conducted or study product is administered. The Assessment of Understanding quiz will be completed before the study consent is signed.

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

### 8.2 Risks and Benefits

#### 8.2.1 Risks

VRC-HIVMAB080-00-AB or VRC-HIVMAB075-00-AB: The first human clinical trials of predecessor VRC01 MAb determined that VRC01 is safe for further evaluation in HIV-1 infected and healthy adults. The solicited local and systemic signs and symptoms following administration of VRC01 were generally none to mild. Some mild transient changes included elevated creatinine, elevated transaminases, neutropenia, and proteinuria. The SC administrations were sometimes

associated with mild transient local reactions (Section 1.3.1). In the ongoing clinical trial VRC 606, VRC01LS is administered to healthy adults who reported mostly mild solicited adverse events (Section 1.3.2). VRC07-523LS is currently being evaluated in healthy adults in a Phase I dose escalation study, VRC 605. There have been no SAEs and no study safety pauses for AEs. VRC 607/A5378 is the first study to evaluate IV administrations of VRC-HIVMAB080-00-AB (VRC01LS) and VRC-HIVMAB075-00-AB (VRC07-523LS) in HIV-1 infected adults.

Administration of some MAbs may cause immune reactions such as acute anaphylaxis, serum sickness, and the generation of antibodies. However, these reactions are rare and more often associated with MAb targeted to human proteins or with the use of murine MAbs which would have a risk of human anti-mouse antibodies [22]. In this regard, as VRC01LS and VRC07-523LS are targeted to a viral antigen and are human MAbs, they are expected to have a low risk of such side effects.

Typically, the side effects of MAbs are mild but 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 [22]; however, this is not expected to be a risk for MAbs like VRC01LS and VRC07-523LS 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) [23]. Most infusion-related events occur within the first 24 hours after beginning administration. Severe reactions, such as anaphylaxis, angioedema, bronchospasm, hypotension, and hypoxia, are infrequent and more often associated with MAbs targeted to human proteins or when non-human MAbs, such as a murine MAb, is used [22]. Specifically, with regard to CRS reactions, these most commonly occur within the first few hours of beginning the infusion and are more common with the first MAb infusion received. This is because the cytokine release is associated with lysis of the cells targeted by the MAb and the burden of target cells is greatest at the time of the first MAb treatment. With licensed therapeutic MAbs, CRS is managed by temporarily stopping the infusion, administering histamine blockers, and restarting the infusion at a slower rate [24].

Delayed allergic reactions to other MAbs may include a serum sickness type of reaction, which may include rash, fever, lymph node enlargement, and joint pains. These symptoms may not appear until several days after the exposure to the MAb and is noted to be more common with chimeric types of MAbs rather than with human MAbs such as VRC01LS and VRC07-523LS [22].

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 participant’s eligibility for other future MAb studies.

Risks of Blood Drawing: Blood drawing may cause pain and bruising and may, infrequently, cause a feeling of lightheadedness or fainting. Rarely, it may cause infection at the site where the blood is taken. In this study, an IV line that can be used for the collection of blood may be 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.

### 8.2.2 Benefits

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

## 8.3 Institutional Review Board

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

The investigator must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the ICF. The investigator will notify the IRB of unanticipated problems, non-compliance, deviations from the protocol, and serious SAEs as described in Section 5.4.

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

## 8.4 Protocol Registration

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol ICF(s) approved, by the appropriate IRB/ethics committee (EC) and any other applicable regulatory entity (RE). Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

Site-specific ICF(s) *WILL* be reviewed and approved by the DAIDS PRO and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Upon receiving final IRB/EC and any other applicable RE approval(s) for an amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all the required documents have been received. Site-specific ICF(s) *WILL NOT* be reviewed and approved by the DAIDS PRO and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration

packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual.

## 8.5 PARTICIPANT CONFIDENTIALITY

The investigator must ensure that no information identifying the participant will be released to any unauthorized party. Individual identifying information will not be included in any reports. Participants 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 participants that the above-named representatives will review their study-related records without violating the confidentiality of the participants.

### 8.5.1 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.

## 8.6 PLAN FOR USE AND STORAGE OF BIOLOGICAL SAMPLES

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

### 8.6.1 Use of Samples, Specimens and Data

Samples, specimens, and data collected under this protocol may be used to conduct protocol-related safety and immune response evaluations, exploratory laboratory evaluations related to the type of infection the study product was designed to prevent, 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 was included in the study ICF.

### 8.6.2 Storage and Tracking of Blood Samples and Other Specimens

All of the stored study research samples will be labeled by a code (such as a number) that only the study site can link to the participant. Samples will be stored in secure facilities with controlled access at the sites. The NIAID Vaccine Immune T-Cell and Antibody Laboratory (NVITAL) in

Gaithersburg, MD, under the direction of the VRC, NIAID, NIH (Bethesda, MD) will serve as a central repository for stored samples. Samples collected for research may be transferred for testing to the VRC/NIAID/NIH, other approved collaborators, or contract laboratories. Data will be kept secure. Only approved investigators or their designees will have access to samples and data.

In the future, other investigators (both at NIH and outside) may wish to study these samples and/or data. Regulatory approval through the proper human participants' protection agency will be sought prior to any sharing of samples that constitutes human participant research. The research use of stored, unlinked, or unidentified samples may be exempt from the need for IRB review and approval. When appropriate, exemption may be obtained through the proper regulatory procedures.

## 8.7 PARTICIPANT IDENTIFICATION AND ENROLLMENT OF STUDY PARTICIPANTS

All study activities will be carried out at the study site. In Part A, study participants 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). In Part B, study participants will be recruited and screened following the screening evaluations in this protocol. 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 70 years of age at enrollment.

### 8.7.1 Participation of Children

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

### 8.7.2 Participation of Site Employees

Clinic sites will follow institutional policy regarding participation of site employees in VRC 607/A5378. Site-specific policies related to employee involvement in research protocols have been provided to the NIAID IRB.

NIH- Specific Employee Participation

NIH employees and members of their immediate families may participate in this protocol. We will follow the Guidelines for the Inclusion of Employees in NIH Research Studies and will give each employee a copy of the "NIH Information Sheet on Employee Research Participation" and a copy of the "Leave Policy for NIH Employees Participating in NIH Medical Research studies." Neither participation nor refusal to participate will have an effect, either beneficial or adverse, on the participant's employment or work situation. The NIH information sheet regarding NIH employee research participation will be distributed to all potential participants who are NIH employees. The employee participant's privacy and confidentiality will be preserved in accordance with NIH Clinical Center and NIAID policies. For NIH employee participants, 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 participant, independent monitoring of the consent process will be included through

the Bioethics Consultation Service. Protocol study staff will be trained on obtaining potentially sensitive and private information from co-workers or subordinates.

### 8.8 Compensation

Compensation for time and inconvenience of study participation will be provided to participants in accordance with the local site-specific guidelines as outlined in the IRB approved site-specific Informed Consent. The total compensation for the participant is based on the number of study clinic visits, injections completed, and other protocol-related activities.

### 8.9 Safety Monitoring

Close cooperation between the designated members of the Protocol Team will occur to evaluate and respond to individual AEs in a timely manner. The VRC designated Safety Officer for the day conducts a daily safety review of clinical data per VRC Standard Operating Procedures. The Protocol Safety Review Team (PSRT), comprised of the Study Chair, PI(s), Associate Investigators, Study Coordinator, Protocol Specialists, other Study Clinicians, DAIDS MO, and an ISM, will review the summary study safety data reports on a weekly basis through 4 weeks after the last participant receives the last product administration, in order to be certain that the study product has an acceptable safety profile, and will continue to monitor the study safety data reports on a monthly basis through completion of the last study visit.

## 9. ADMINISTRATIVE AND LEGAL OBLIGATIONS

### 9.1 Protocol Amendments and Study Termination

Protocol Amendments must be made only with the prior approval of the DAIDS/NIAID, VRC, and ACTG. Agreement from the protocol team and DAIDS Medical Officer (MO) must be obtained for all protocol amendments and amendments to the ICF. All study amendments will be submitted to the IRB for approval.

The DAIDS, VRC, ACTG, the NIAID or local IRB (as applicable), the Office of Human Research Protections, the 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.

### 9.2 Study Documentation and Storage

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

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

The PI and staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives

from the DAIDS/NIAID, VRC, ACTG, IRB, FDA, and/or other local, US, and international regulatory entities. Elements include:

- Participant files containing completed ICF, and supporting copies of source documentation (if kept).
- Study files containing the protocol with all amendments, IBs, and copies of all correspondence with the IRB, the NIAID's Division of AIDS and Vaccine Research Center, and ACTG.

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 2 years after marketing approval or refusal (21 CFR 312.62). No study document should be destroyed without prior written agreement between the NIAID's Division of AIDS, VRC, ACTG, 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 DAIDS/NIAID, VRC, and ACTG in writing of the new responsible person and/or the new location.

## 9.3 Study Monitoring, Data Collection and Data Sharing

### 9.3.1 Study Monitoring

The DAIDS/NIAID and VRC/NIAID monitors and regulatory authorities inspectors (if applicable) or their authorized representatives are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the trial, provided that participant confidentiality is respected.

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

Site investigators will allow the study monitors, the NIAID or local IRB (as applicable), FDA, and other local, US or international regulatory entities to inspect study documents (e.g., consent forms, drug distribution forms, case report forms) and pertinent hospital or clinic records for confirmation of the study data.

### 9.3.2 Data Collection

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

### 9.3.3 Data Sharing

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

## 9.4 LANGUAGE

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

## 9.5 POLICY REGARDING RESEARCH-RELATED INJURIES

The study site will provide short-term medical care for any injury resulting from participation in this research. In general, the National Institutes of Health, the Clinical Center, or the U.S. Federal Government will provide no long-term medical care or financial compensation for research-related injuries.

## 9.6 MULTI-SITE MANAGEMENT

For Part A, the Vaccine Research Center, NIAID, NIH is the coordinating center as well as a site for this protocol.

For Part B, the ACTG Network Coordinating Center will function as the coordinating center.

The protocol plan for previous versions of the protocol was to establish a Reliance Agreement with each collaborating study site such that the NIAID IRB is the IRB of Record for the conduct of the VRC 607/A5378 protocol (Part A). A reliance agreement was established for the University of Pennsylvania for the previous protocol versions and will continue to be effective for version 4 of the protocol. However for Part B, the participating ACTG sites are not expected to establish a reliance agreement and will use their local IRB as the IRB of Record for the conduct of VRC 607/A5378 Version 4.0 at their site.

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# APPENDIX I

# STUDY INFORMED CONSENT TEMPLATE

TITLE: VRC 607/ACTG A5378: A Phase 1, Single Dose Study of the Safety and Virologic Effect of an HIV-1 Specific Broadly Neutralizing Human Monoclonal Antibody, VRC-HIVMAB080-00-AB (VRC01LS) or VRC-HIVMAB075-00-AB (VRC07-523LS), Administered Intravenously to HIV-Infected Adults.

INTRODUCTION

We invite you to take part in a research study at the [insert institution's name]. This study is a collaboration between the Vaccine Research Center (VRC), NIAID, NIH and the AIDS Clinical Trials Group (ACTG).

First, we want you to know that:

- Taking part in this study 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. You will be treated the same no matter what.
- If you are at the NIH and would like 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.
- We will tell you about new information from this study or other studies that may affect your health, welfare, or willingness to stay in this study. If you want the results of the study, let the study staff know.

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

In this study, we are testing two experimental products or drugs called "VRC01LS" and "VRC07-523LS". Experimental means that these products have not been approved by the U.S. Food and Drug Administration (FDA), but the FDA has allowed us to test them in research studies. VRC01LS and VRC07-523LS are antibodies directed against HIV virus. The main purpose of this study is to see if these antibodies are safe and how your body will respond to them. (An antibody is a type of protein that helps protect the body against foreign matter, such as bacteria and viruses; it can be either produced by your body or made in a laboratory.)

There are two different parts in this study (Part A and Part B). In Part A, 7 people got VRC01LS. In Part B, 7 people (up to 10 people) will get VRC07-523LS. People were put in Part A first and now Part A of the study is done. People will now be put in Part B. If you agree to take part in this study (Part B), you will get VRC07-523LS only and we will measure the amount of the drug in your body and how much stays in your body over time. We will check to see if your immune system makes antibodies against the product you get.

About 14 to 20 people (7 to 10 people in each part) will take part in this study at the NIH Clinical Center in Bethesda, Maryland and sites within the ACTG Network. The study will include a total of 23 clinic visits per person over a period of about 11 months.

You will be able to start 3-drug antiretroviral therapy (prescribed by your primary HIV clinician; not study-provided) after you have completed the day 14 study procedures. We strongly advise that you start antiretroviral therapy after you have completed this stage of the study.

## STUDY PRODUCTS

VRC01LS and VRC07-523LS are study products that contain monoclonal antibodies. "Monoclonal" means that all antibodies in each product are exactly the same. These antibodies target the virus that causes HIV infection. As of May 10, 2018, approximately 60 people have received one of these antibodies and have not had any serious side effects or safety concerns.

In other research studies, over 840 adults with or without HIV-infection got other monoclonal antibodies similar to VRC01LS and VRC07-523LS, without serious side effects.

VRC01LS and VRC07-523LS are based on an antibody that was first found in an HIV-infected person. Both of these study products were developed by the Vaccine Research Center (VRC), NIH and made in a drug manufacturing laboratory. There are currently research studies of these products in adults without HIV infection. This is the first study to give VRC01LS or VRC07-523LS to people with HIV infection.

There is currently no cure for HIV. We do not expect the products in this study to cure or control your HIV.

In laboratory and animal studies, VRC01LS and VRC07-523LS were shown to attach to and inactivate many types of HIV viruses. It is not known if the products will act the same way when given to humans. It will take many studies to learn if the products are useful for preventing or treating HIV. This study alone will not answer this question.

SCREENING VISIT

If you decide to join this study, you will be asked to sign this consent form. After you have signed the form, you will be asked some questions and will undergo some tests at the screening visit to see if it is safe for you to join the study.

At the screening visit you will have a physical exam. You will be asked about your medical history, including your HIV history, any medicines you have taken in the past and are currently taking, and if you have ever received antibodies directed against the HIV virus or taken any anti-HIV medicines. We will draw about 6 tubes of blood from you for routine blood tests, tests for Hepatitis B virus or Hepatitis C virus infection, tests for HIV antibodies and viral load (the amount of HIV in your blood), and $CD4^+$/$CD8^+$ T cell count (cells in your blood that fight infection). You will be informed if any tests show a medical problem. You will be advised if results show that you should seek medical care. Some medical conditions may make you not eligible for a clinical trial of an investigational product.

If you are female and able to become pregnant, you will have a pregnancy test done to see if you are pregnant. You cannot participate in this study if you are pregnant. If you are not pregnant or you are having sex that could lead to pregnancy, you will be asked and must agree to use birth control before you are able to participate in this study. We will discuss effective birth control methods with you.

ELIGIBILITY

You are eligible to participate in this study if you have completed the screening process and are:

- 18 to 70 years old
- HIV infected, have never taken antiretroviral (ARV) medications, but otherwise in good general health
- Under the care of a primary care provider for management of HIV
- Willing to let the study team give your lab test results to your primary care provider while you are in this study.
- Willing to receive VRC07-523LS
- Willing to donate blood samples for future research
- Willing to use birth control for the whole study, if you are able to become pregnant

STUDY PROCEDURES

Study product infusion: If you agree to enroll in this study, you will get one dose of VRC07-523LS. The exact dose you get will depend on how much you weigh.

Before you are given the study product, your temperature, blood pressure, heart rate, and weight will be taken. You may also have a brief physical exam. If you are female and able to become pregnant, you must use an effective form of birth control for the entire study. A pregnancy test will be done to see if you are pregnant. If you are pregnant, we will not give you the study product.

VRC07-523LS will be given to you by intravenous (IV) infusion. This means we will place a thin tube or IV line into a vein in your arm. The IV line will be attached to a bag that contains the study product mixed with a liquid called "normal saline" or salt water. It will flow into your vein for about 30 minutes. If you have side effects during the infusion, it will be slowed or stopped as needed. You will be observed for at least 30 minutes immediately after receiving the study product.

If possible, we will also place an IV line in your other arm to collect blood samples. We will draw your blood before and right after the infusion, then at least 5 more times over the next 4 hours from this IV line. There are other blood draws at 8, 12, and 36 hours after infusion, which are optional. At least one IV line will stay in your arm for several hours. You will not lose any benefits if you choose not to give the optional blood samples. If you choose to get these blood draws, you may be admitted to the hospital for an overnight stay. The hospital stay is for convenience only and not to give you care or treatment.

We will give you a thermometer and ask you to check your temperature every day for 3 days after you get the study product. You will need to record your temperature and any symptoms you may have. Even if you do not feel sick, it is still very important that you record this information. You will get a password to a secure website to enter this information on an electronic form or "diary". If you do not have a computer, you may use a paper diary instead.

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

Follow-up visits: After you get the study product, you will need to come back to the clinic 11 times over a 4-week period. During the next 9 months, you will have 10 more follow-up visits.

At most visits, we will check you for any health changes or problems. Your temperature, blood pressure, and pulse will be taken and you will have a physical exam. We will ask you how you are feeling and if you have taken any medications. We will also provide pregnancy prevention counseling (counseling to prevent pregnancy) and positive prevention counseling (counseling to prevent illness and promote good health in people who know they are HIV-positive) while you are in the study.

We will draw about 1 to 11 tubes of blood from you at each visit, depending on the type of visit. We will also ask you to provide a urine sample for a urine test at most visits. We will tell you right away if any of your test results show a health problem. You might need to have extra clinic visits and laboratory tests if you have health changes that need to be checked. The total amount of blood we draw from you will meet NIH guidelines.

We will use some blood samples to see how long the study product remains in your body and if your immune system makes antibodies against it. Results of these tests are not for checking on your health and we will not give you these results. We may also use some blood samples to check the level of ARV medications in your blood while you are in this study.

Research studies follow a set schedule. This helps us answer the research questions. The visit schedule is a little flexible, but it is important that you work with the staff to follow the schedule as closely as possible. You should try not to miss any visits. You should contact the clinic staff as soon as possible if you need to change the date or time of any visit.

For the entire duration that you are on study, which will be 48 weeks or about 11 months, a maximum of about 922 mL (or about 2 pints) of blood will be collected.

## HIV TESTING AND MANAGEMENT

As you take part in this study, you will have frequent testing of your HIV viral load and $CD4^+$ T cell count for research purposes. These test results will be given to you and sent to your primary care provider. You should discuss these results and any questions about management of your HIV infection with your primary care provider.

This study does not include standard medical care or management of your HIV infection. The U.S. Department of Health and Human Services and the clinical research team recommend that all HIV-infected individuals take (ARV) medication to reduce the chance of getting sick from HIV, increase life expectancy with HIV infection, and prevent the spread of HIV to others.

We will not give you ARV medications as part of this research study. You must have a primary health care provider for HIV to take part in this study. If you do not have one and need help finding one or getting ARV medications, please tell a study doctor or nurse. We will help you find a qualified HIV doctor and ARV medications. You and your primary health care provider will make all decisions about starting, stopping, or changing ARV medications. However, we strongly advise that you start ARV medications after you have completed the day 14 study procedures. We expect you to tell us about changes in your ARV medications. We do not expect VRC07-523LS to control HIV by itself. You should not change or stop ARV treatment without talking about it with your primary care provider. Changes in ARV treatment will not affect your continued participation in the study.

## 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, study product infusions may be delayed or canceled.

GENETIC TESTING

In the future, genetic research tests may be done on your stored samples to help understand how VRC07-523LS works and interacts with your body. In research studies, genetic tests are done to see if different types of immune response are related to genetic differences in people, this includes testing your antibody genes. Genetic tests done in a research lab from your stored samples will not be recorded in your medical record and will not have your name on the sample. The performance of these tests is not for health care purposes.

HLA type is a genetic test. People with certain HLA types might be more likely to develop certain diseases. Simply having those HLA types does not mean they will develop those diseases. HLA typing can reveal family relationships. It is our policy not to discuss your HLA results unless they have direct medical or reproductive implications for you or your family. Genetic information about you will not be revealed to others, including your relatives, without your permission. We will not release any information about you or your family to any insurance company or employer unless you sign a document allowing release of information.

VRC clinic only: HLA typing may be ordered through the NIH Clinical Center medical laboratory. If performed at the NIH Clinical Center, your HLA results will be in your medical record.

STORED SAMPLES

We will collect blood samples 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 done with your stored samples will not be in your medical record or reported to you.

Some of your blood samples that are left over after all required study testing are done may be stored and used for VRC-approved and ACTG-approved HIV-related research.

Labeling of Stored Samples: We will label your stored samples by a code (like a number). Only the study team can link this code to you. Any identifying information about you will be kept confidential as much as the law allows. 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; in the ACTG or outside of the ACTG) 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 can only take part in this study if you agree to let us collect, store, and use your blood samples in future unspecified research. If you decide not to take part in this study, you may still take part in other studies at the NIH or at the research site.

## POSSIBLE STUDY RISKS

Risks of Blood Drawing and IV insertion: The risks of drawing blood from a vein and having an IV include pain, bruising, bleeding, lightheadedness and fainting. Rarely, infection or inflammation can occur in the skin or vein. Blood clots are possible risks when using an IV for blood draw.

Risks of VRC07-523LS: This study is the first time that VRC07-523LS is being given to people with HIV infection. As of January 2018, the people who have received at least one dose of VRC07-523LS had no concerning reactions to the product. VRC07-523LS may have other unknown risks or side effects. We do not know if getting VRC07-523LS will affect how you respond to any similar monoclonal antibody against HIV.

General risks of monoclonal antibodies: Side effects to infusions of monoclonal antibodies 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 product is infused. If you have symptoms while you get VRC07-523LS, tell the nurse right away. Slowing or stopping the infusion may help improve these symptoms. Side effects may also include reactions at the injection site, such as redness, bruising, and swelling.

Some antibody products have a risk of serious allergic reactions or cytokine release syndrome 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.
- Cytokine release syndrome can happen when an antibody targets a cell protein that triggers immune cells to release cytokine (proinflammatory molecules in your body).

All of these reactions are very unlikely because VRC07-523LS is a fully human antibody that attacks the HIV virus, and not your cells.

In addition to the possible risks that are listed above, the study products may have other side effects that we do not know about yet. Taking part in this study may affect your eligibility for future studies of other experimental monoclonal antibodies, antibody mixtures or other similar products.

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 during Pregnancy: We do not know what effects the study products may have on a fetus or nursing infant. Women must agree not to get pregnant during the study. We will discuss effective birth control methods with you. If you are able to become pregnant, you and your partner must use reliable birth control from the time you start the study until you complete the last study visit.

If you can become pregnant, you must have a pregnancy test before you enter this study. The test must show that you are not pregnant. You must tell the clinic staff right away if you become pregnant during this study or think that you might be pregnant. If you become pregnant after getting the study product, 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). This report will not use your name or other information that could be used to identify you.

## 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 YOUR PARTICIPATION

There are no costs to you for taking part 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. It is possible that you may have some expenses that are not covered by the study compensation provided.

## COMPENSATION TO YOU FOR YOUR PARTICIPATION

You will be compensated [insert site IRB-approved amount] for your study participation as follows: [insert site plan]. This will be based on the number and type of study visits that you complete.

## REASONS FOR REMOVING YOU FROM THE STUDY WITHOUT YOUR CONSENT

You may be removed from the study for several different reasons, including:

- You do not keep appointments or follow study procedures.
- You get a serious illness that needs ongoing medical care.
- 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, you will be told the reason why.

You may choose to stop taking part in the study at any time.

If you received the study product before you discontinue the study early, you will be asked to continue to be part of the study and return for the rest of the study visits. At the visits you will have some tests performed for safety monitoring, however samples for research purposes will not be collected.

## ALTERNATIVES

This study is not designed to treat or prevent HIV infection or any disease. You may choose to not take part in this study. You may be eligible for other studies. Instead of being in this study you have the choice of:

- Treatment with prescription drug available to you
- Treatment with experimental drugs, if you qualify
- No treatment

Please talk to your doctor about these and other choices that may be available to you. Your doctor will explain the risks and benefits of these choices.

## CONFLICT OF INTEREST

The research staff are reviewed at least yearly for conflicts of interest. You may ask the research team for additional information.

The National Institutes of Health, including some members of the Vaccine Research Center scientific staff, developed the experimental product in this research study. The results of this study could play a role in whether the FDA will approve the experimental product for sale at some time in the future. If approved, the future sale of the vaccine 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 get any money from the development or sale of the product.

This protocol 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.

## CLINICALTRIALS.GOV

A description of this clinical trial will be available on http://www.ClinicalTrials.gov. This web site 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, members of Congress, law enforcement officials, National Institute of Allergy and Infectious Diseases institutional review board, study monitors, or other authorized people.

ACTG Clinical Research Sites: We will do everything we can to protect your privacy. In addition to the efforts of the study staff to help keep your personal information private, we have gotten a Certificate of Confidentiality from the U.S. Federal Government. This certificate means that researchers cannot be forced to tell people who are not connected with this study, such as the court system, about your participation. Also, any publication of this study will not use your name or identify you personally.

Your records may be reviewed by the U.S. Food and Drug Administration (FDA), the ACTG, the U.S. Office for Human Research Protections (OHRP), or other local, US, and international regulatory entities as part of their duties (insert name of site) institutional review board (IRB) (a committee that protects the rights and safety of participants in research), National Institutes of Health (NIH), study staff, study monitors, and their designees. Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study.

Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to yourself or others, we will be required to tell the proper authorities.

2. Policy Regarding Research-Related Injuries.

The [insert institution's name] will provide short-term medical care for any injury resulting from your participation in research here. The cost of this treatment will be charged to you or your insurance company. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the [insert institution's name], National Institutes of Health, 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 participants is guided by the National Institutes of Health policies or as approved by the Institutional Review Board (IRB) of the clinical research site.

4. Problems or Questions.

If you have any problems or questions about this study or about any research-related injury, contact the Principal Investigator, [insert site PI name], or the Study Coordinator, [study coordinator name] at [contact phone number].

If you have any questions about your rights as a research participant, you may contact:

VRC Clinic only: The Clinical Center Patient Representative at 301-496-2626.

ACTG Clinical Research Sites:

- Name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site
- Telephone number of above

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<br>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. | |
| Signature of Adult Participant/Legal Representative | Date |
| Print Name | Time |
| THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM XXXXXX THROUGH XXXXXX. | |
| Signature of Investigator/Person Obtaining Consent | Signature of Witness |
| Date | Date |
| Print Name | Print Name |

# APPENDIX II

# CONTACT INFORMATION

# APPENDIX III

# SCHEDULE OF EVALUATIONS

| Schedule of Evaluations Part A | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit Number | | | 01R | 02 | 02A | 02B | 02C | 02D | 02E | 02F | 02G | 02H | 03 | 03A | 04 | 05 | 06 | 07 |
| Time After Day 0 Infusion | | | | Pre | EOI | 30 | 1hr | 2hr | 3h | 4hr | 8hr | 12hr | 24hr | 36hr | 48hr | 72hr | Wk1 | Wk1 |
| Day of Study | | | -28 to 0 | D0 | D0 | D0 | D0 | D0 | D0 | D0 | D0 | D0 | D1 | D1 | D2 | D3 | D5 | D7 |
| Study Procedures | Tube | Screen | Enroll | Outpatient (with optional inpatient admission) | | | | | | | | | | | | | | |
| VRC 500 Screening Consent | | X | | | | | | | | | | | | | | | | |
| VRC 607/A5378 Assessment of Understanding; Consent | | | X | | | | | | | | | | | | | | | |
| [1] Physical exam | | X | X | X | X | | | | | | | | X | | X | | | X |
| [2] Medical history | | X | X | X | | | | | | | | | X | | X | | | X |
| [3] Concomitant Medications | | X | X | X | | | | | | | | | X | | X | | | X |
| [4] ARV Medication Record | | X | X | X | | | | | | | | | | | | | | |
| Study Product Administration | | | | X | | | | | | | | | | | | | | |
| [5] Diary "Card" Reactogenicity Review | | | | X | | | | | | | | | | | | X | | |
| Pregnancy prevention counseling | | X | X | X | | | | | | | | | | | | | | |
| Positive prevention counseling | | X | X | | | | | | | | | | | | | | | |
| Clinical Labs | | | | | | | | | | | | | | | | | | |
| CBC, platelets | EDTA | 3 | | 3 | | | | | | | | | | | 3 | | | 3 |
| ALT, AST, ALP, creatinine | GLT | 4 | | 4 | | | | | | | | | | | 4 | | | 4 |
| Hepatitis BsAg | SST | 4 | | | | | | | | | | | | | | | | |
| Hep C viral load | SST | 4 | | | | | | | | | | | | | | | | |
| [6] Pregnancy test: urine or serum | | X | X | X | | | | | | | | | | | | | | |
| HIV EIA | SST | 4 | | | | | | | | | | | | | | | | |
| HIV PCR | EDTA | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| $CD4^+/CD8^+$ | EDTA | 3 | | 3 | | | | | | | | | | | | | | 3 |
| Research Samples | | | | | | | | | | | | | | | | | | |
| Timed PK samples | SST | | | 4 | 4 | 4 | 4 | 4 | 4 | 4 | | | 4 | | 4 | | | 4 |
| PBMC and plasma | EDTA | | 20 | | | | | | | | | | | | 10 | | | 20 |
| Serum | SST | | 24 | | | | | | | | | | | | 8 | | | 16 |
| Daily Volume (mL) | | 28 | 50 | 20 | 10 | 10 | 10 | 10 | 10 | 10 | 6 | 6 | 10 | 6 | 35 | 6 | 6 | 56 |
| Cumulative Volume (mL) | | 28 | 78 | 98 | 108 | 118 | 128 | 138 | 148 | 158 | 164 | 170 | 180 | 186 | 221 | 227 | 233 | 289 |

"Visits" 02G, 02H and 03A are optional

SCHEDULE OF EVALUATIONS (continued):

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

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

[3] Concomitant medications: Concomitant medications must be entered in the database at enrollment and updated as required in Section 4.2.8.

[4] ARV medication record: ARVs will be reviewed with the participant throughout the study, however the ARV medication record will be documented in the research chart and database as indicated and whenever changes are reported.

[5] Diary card reactogenicity review: Participants will begin to record 3-day reactogenicity as noted in Section 4.2.4. Clinicians will review with the participant at a minimum on Day 3 and prior to Day 3 as needed. If any reported reactogenicity is unresolved by Day 3, it will continue to be reviewed with the participant at each visit until resolved. Data from the data will be recorded in the database as noted in Section 4.2.4.

[6] Pregnancy test: Negative pregnancy test results must be confirmed for women of reproductive potential prior to study product administration.

Visit Windows:

Screening: evaluations for eligibility must be completed within 28 days of enrollment as noted in Section 4.1.

Visit 01R and Day 0: Visit 01R may be done on the same day as Day 0. Day 0 = day of product administration. Day 0 is preferably scheduled within 14 days after enrollment at "Visit 01R", but may be scheduled up to 28 days after enrollment. Day 0 evaluations prior to VRC01LS administration are the baseline for assessing subsequent AEs.

EOI = End of Infusion Blood draw "visits," defined by minutes or hours after an infusion are relative to the exact time of the end of infusion (EOI). The exact time of start (T0), EOI and each PK draw is recorded to ensure accurate PK analysis.

Visit 02A: up to 10 minutes post EOI

Visit 02B & 02C: ± 10 minutes

Visits 02D – 02F: ± 15 minutes

Visit 02G: ± 30 minutes *Note: This visit is optional.*

Visit 02H, 03, 03A: ± 1 hour *Note: Visits 02H and 03A are optional.*

Visit 04: ± 6 hours

Visit 05: ± 12 hours

Visits 06 – 07: ± 1 day

| Schedule of Evaluations Part A (continued) | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit Number | | 08 | 09 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 |
| Week of Study | | Wk2 | Wk2 | Wk2 | Wk3 | Wk3 | Wk4 | Wk5 | Wk6 | Wk7 | Wk8 | Wk12 | Wk16 | Wk20 | Wk24 | Wk36 | Wk48 |
| Day of Study | | D9 | D12 | D14 | D16 | D21 | D28 | D35 | D42 | D49 | D56 | D84 | D112 | D140 | D168 | 252 | 336 |
| Study Procedures | Tube | | | | | | | | | | | | | | | | |
| [1] Physical exam | | | | X | | X | X | X | X | X | X | X | X | X | X | X | X |
| Interim medical history | | | | X | | X | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant medications | | | | X | | X | X | X | X | X | X | X | X | X | X | X | X |
| ARV medication record | | | | X | | X | X | X | X | X | X | X | X | X | X | X | X |
| Pregnancy prevention counseling | | | | | | | | | | | | | | | X | | |
| Positive prevention counseling | | | | | | | X | | | | | | | | X | X | X |
| Clinical Labs | | | | | | | | | | | | | | | | | |
| CBC, platelets | EDTA | | | 3 | | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| ALT, AST, ALP, creatinine | GLT | | | 4 | | | 4 | | | | | 4 | | | 4 | 4 | 4 |
| Pregnancy test: urine or serum | | | | | | | | | | | | | | | X | | X |
| HIV PCR | EDTA | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| $CD4^+/CD8^+$ | EDTA | | | 3 | | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| [2] HLA typing (VRC Clinic only) | EDTA | | | | | | | | | | | | | 20 | | | |
| Research Samples | | | | | | | | | | | | | | | | | |
| [3] PK samples | SST | | | 4 | | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| PBMC and plasma | EDTA | | | | | | 20 | 20 | | | 20 | 20 | | | 20 | 20 | 20 |
| Serum | SST | | | | | | 24 | 16 | | | 24 | 24 | 24 | 24 | 24 | 24 | 24 |
| Daily Volume (mL) | | 6 | 6 | 20 | 6 | 16 | 64 | 52 | 16 | 16 | 60 | 64 | 40 | 60 | 64 | 64 | 64 |
| Cumulative Volume (mL) | | 295 | 301 | 321 | 327 | 343 | 407 | 459 | 475 | 491 | 551 | 615 | 655 | 715 | 779 | 843 | 907 |

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

[2] HLA type blood sample is collected once in the study at the VRC Clinic; 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.

[3] PK samples: PK samples will be optional at visits 22 and 23 if VRC01LS levels are undetectable at the PK draw at visit 21.

Visit windows: Visits 08 – 11: ± 1 day; Visits 12 – 17: ± 2 days; Visits 18 – 20: ± 5 days; Visits 21 -23: ± 7 days

| Schedule of Evaluations Part B | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit Number | | | 01R | 02 | 02A | 02B | 02C | 02D | 02E | 02F | 02G | 02H | 03 | 03A | 04 | 05 | 06 | 07 |
| Time After Day 0 Infusion | | | | Pre | EOI | 30 | 1hr | 2hr | 3h | 4hr | 8hr | 12hr | 24hr | 36h | 48h | 72hr | Wk1 | Wk1 |
| Day of Study | | | -10 to 0 | D0 | D0 | D0 | D0 | D0 | D0 | D0 | D0 | D0 | D1 | D1 | D2 | D3 | D5 | D7 |
| Study Procedures | Tube | Screen | Enroll | Outpatient (with optional inpatient admission) | | | | | | | | | | | | | | |
| VRC 607/A5378 Assessment of Understanding; Consent | | X | | | | | | | | | | | | | | | | |
| [1] Physical exam | | X | X | X | X | | | | | | | | X | | X | | | X |
| [2] Medical history | | X | X | X | | | | | | | | | X | | X | | | X |
| [3] Concomitant Medications | | X | X | X | | | | | | | | | X | | X | | | X |
| [4] ARV Medication Record | | X | X | X | | | | | | | | | | | | | | |
| [5] Study Product Administration | | | | X | | | | | | | | | | | | | | |
| [6] Diary "Card" Reactogenicity Review | | | | X | | | | | | | | | | | | X | | |
| Pregnancy prevention counseling | | X | X | X | | | | | | | | | | | | | | |
| Positive prevention counseling | | X | X | | | | | | | | | | | | | | | |
| Clinical Labs | | (numbers indicate volume of blood and urine sample to be collected) | | | | | | | | | | | | | | | | |
| CBC, platelets | EDTA | 3 | | 3 | | | | | | | | | | | 3 | | | 3 |
| ALT, AST, ALP, creatinine | GLT | 4 | | 4 | | | | | | | | | | | 4 | | | 4 |
| Hepatitis BsAg | SST | 4 | | | | | | | | | | | | | | | | |
| Hep C viral load | SST | 4 | | | | | | | | | | | | | | | | |
| [7] Pregnancy test: urine or serum | URN | 5 | 5 | 5 | | | | | | | | | | | | | | |
| | SST | 3 | 3 | 3 | | | | | | | | | | | | | | |
| HIV EIA | SST | 4 | | | | | | | | | | | | | | | | |
| HIV PCR | EDTA | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| $CD4^+/CD8^+$ | EDTA | 3 | | 3 | | | | | | | | | | | | | | 3 |
| Urinalysis | | | 5 | | | | | | | | | | | | | | | |
| Research Samples | | (numbers indicate volume of blood sample to be collected) | | | | | | | | | | | | | | | | |
| Timed PK samples | SST | | | 4 | 4 | 4 | 4 | 4 | 4 | 4 | | | 4 | | 4 | | | 4 |
| PBMC and plasma | EDTA | | 20 | | | | | | | | | | | | 10 | | | 20 |
| Serum | SST | | 24 | | | | | | | | | | | | 8 | | | 16 |
| Daily Blood Volume (mL) | | 28-31 | 50-53 | 20-23 | 10 | 10 | 10 | 10 | 10 | 10 | 6 | 6 | 10 | 6 | 35 | 6 | 6 | 56 |
| Maximum Cumulative Blood Volume (mL) | | 31 | 84 | 107 | 117 | 127 | 137 | 147 | 157 | 167 | 173 | 179 | 189 | 195 | 230 | 236 | 242 | 298 |

"Visits" 02G, 02H, and 03A are optional

SCHEDULE OF EVALUATIONS (continued):

[1] Physical exam: Screening includes complete physical exam with vital signs, height and weight. Day 0 physical exam includes vital signs (blood pressure, temperature and pulse) and weight. At other visits if medically indicated, a targeted exam is performed. Weight must be measured at enrollment (Visit 01R), which will be used for ordering the study product based on a "mg/kg" dose. Otherwise only blood pressure (BP), pulse and temperature are required.

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

[3] Concomitant medications: Concomitant medications must be entered in the database at enrollment and updated as required in Section 4.2.8. Participants will be strongly encouraged to initiate 3-drug ART (prescribed by their primary HIV clinician; not study-provided) after completing day 14 study evaluations. Document them as concomitant medications.

[4] ARV medication record: ARVs will be reviewed with the participant throughout the study, however the ARV medication record will be documented in the research chart and database as indicated and whenever changes are reported.

[5] Study Product Administration: Administration should occur within 10 days after enrollment per Section 4.2.2 and Day 0 visit window details below. Study product should be available on site one day prior to the scheduled infusion (D0). Refer to the MOP for detailed study product ordering instructions.

[6] Diary card reactogenicity review: Participants will begin to record 3-day reactogenicity as noted in Section 4.2.4. Clinicians will review with the participant at a minimum on Day 3 and prior to Day 3 as needed. If any reported reactogenicity is unresolved by Day 3, it will continue to be reviewed with the participant at each visit until resolved. Data from the data will be recorded in the database as noted in Section 4.2.4.

[7] Pregnancy test: Negative pregnancy test results must be confirmed for women of reproductive potential prior to study product administration.

Visit Windows:

Screening: evaluations for eligibility must be completed within 28 days of enrollment as noted in Section 4.1.

Visit 01R and Day 0: Visit 01R may be done on the same day as Day 0. Day 0 = day of product administration. Day 0 should be scheduled within 10 days after enrollment at "Visit 01R". Day 0 evaluations prior to VRC07-523LS administration are the baseline for assessing subsequent AEs.

EOI = End of Infusion Blood draw "visits," defined by minutes or hours after an infusion are relative to the exact time of the end of infusion (EOI). The exact time of start (T0), EOI and each PK draw is recorded to ensure accurate PK analysis.

Visit 02A: up to 10 minutes post EOI

Visit 02B & 02C: ± 10 minutes

Visits 02D – 02F: ± 15 minutes

Visit 02G: ± 30 minutes *Note: This visit is optional.*

Visit 02H, 03, and 03A: ± 1 hour *Note: Visits 02H and 03A are optional.*

Visit 04: ± 6 hours

Visit 05: ± 12 hours

Visits 06 – 07: ± 1 day *Note: These visits cannot occur on the same day. Visit 07 cannot occur on the same day as Visit 08.*

| Schedule of Evaluations Part B (continued) | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit Number | | 08 | 09 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 |
| Week of Study | | Wk2 | Wk2 | Wk2 | Wk3 | Wk3 | Wk4 | Wk5 | Wk6 | Wk7 | Wk8 | Wk12 | Wk16 | Wk20 | Wk24 | Wk36 | Wk48 |
| Day of Study | | D9 | D12 | D14 | D16 | D21 | D28 | D35 | D42 | D49 | D56 | D84 | D112 | D140 | D168 | D252 | D336 |
| Study Procedures | Tube | | | | | | | | | | | | | | | | |
| [1] Physical exam | | | | X | | X | X | X | X | X | X | X | X | X | X | X | X |
| Interim medical history | | | | X | | X | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant medications | | | | X | | X | X | X | X | X | X | X | X | X | X | X | X |
| ARV medication record | | | | X | | X | X | X | X | X | X | X | X | X | X | X | X |
| Pregnancy prevention counseling | | | | | | | | | | | | | | | X | | |
| Positive prevention counseling | | | | | | | X | | | | | | | | X | X | X |
| Clinical Labs | | (numbers indicate volume of blood and urine sample to be collected) | | | | | | | | | | | | | | | |
| CBC, platelets | EDTA | | | 3 | | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| ALT, AST, ALP, creatinine | GLT | | | 4 | | | 4 | | | | | 4 | | | 4 | 4 | 4 |
| Pregnancy test: urine or serum | URN | | | | | | | | | | | | | | 5 | | 5 |
| | SST | | | | | | | | | | | | | | 3 | | 3 |
| HIV PCR | EDTA | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| $CD4^+/CD8^+$ | EDTA | | | 3 | | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| [2] HLA typing (VRC Clinic only) | EDTA | | | | | | | | | | | | | 20 | | | |
| Urinalysis | | | | 5 | | | 5 | | | | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Research Samples | | (numbers indicate volume of blood sample to be collected) | | | | | | | | | | | | | | | |
| [3] PK samples | SST | | | 4 | | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| PBMC and plasma | EDTA | | | | | | 20 | 20 | | | 20 | 20 | | | 20 | 20 | 20 |
| Serum | SST | | | | | | 24 | 16 | | | 24 | 24 | 24 | 24 | 24 | 24 | 24 |
| Daily Blood Volume (mL) | | 6 | 6 | 20 | 6 | 16 | 64 | 52 | 16 | 16 | 60 | 64 | 40 | 60 | 64-67 | 64 | 64-67 |
| Maximum Cumulative Blood Volume (mL) | | 304 | 310 | 330 | 336 | 352 | 416 | 468 | 484 | 500 | 560 | 624 | 664 | 724 | 791 | 855 | 922 |

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

[2] HLA type blood sample is collected once in the study at the VRC Clinic; 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.

[3] PK samples: PK samples will be optional at visits 22 and 23 if VRC07-523LS levels are undetectable at the PK draw at visit 21. If needed, PK assay for ARVs will be performed; however, no additional blood draw is required.

Visit windows: Visits 08 – 11: ± 1 day *(Note: Visit 08 cannot occur on the same day as Visit 07. Visits 09, 10, and 11 cannot occur on the same day.)*; Visits 12 – 17: ± 2 days; Visits 18 – 20: ± 5 days; Visits 21 -23: ± 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 grading table, the Manual for Expedited Reporting of Adverse Events to DAIDS, and supplementary tutorial and tools can be found on the Division of AIDS Regulatory Support Center (RSC) website:

http://rsc.tech-res.com/clinical-research-sites/safety-reporting

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

- Weight loss will be recorded as an adverse event only if it is considered deleterious to the participant's health.

INSTITUTE: National Institute of Allergy and Infectious Diseases

STUDY NUMBER: 16-I-0147 PRINCIPAL INVESTIGATOR: [redacted]

STUDY TITLE: VRC 607/ACTG A5378: A Phase 1, Single Dose Study of the Safety and Virologic Effect of an HIV Specific Broadly Neutralizing Human Monoclonal Antibody, VRC-HIVMAB080-00-AB (VRC01LS) or VRC-HIVMAB075-00-AB (VRC07-523LS) Administered Intravenously to HIV-Infected Adults.

Continuing Review Approved by the IRB on 05/07/18
Amendment Approved by the IRB on 07/09/18 (D) Date Posted to Web: 08/22/18
Study Consent [Version 4.0]

## INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH). This study is a collaboration between the Vaccine Research Center (VRC), NIAID, NIH and the AIDS Clinical Trials Group (ACTG).

First, we want you to know that:

- Taking part in this study 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. You will be treated the same no matter what.
- If you are at the NIH and would like 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.
- We will tell you about new information from this study or other studies that may affect your health, welfare, or willingness to stay in this study. If you want the results of the study, let the study staff know.

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**

In this study, we are testing two experimental products or drugs called "VRC01LS" and "VRC07-523LS". Experimental means that these products have not been approved by the U.S. Food and Drug Administration (FDA), but the FDA has allowed us to test them in research studies. VRC01LS and VRC07-523LS are antibodies directed against HIV virus. The main purpose of this study is to see if these antibodies are safe and how your body will respond to them. (An antibody is a type of protein that helps protect the body against foreign matter such as bacteria and viruses; it can be either produced by your body or made in a laboratory.)

There are two different parts in this study (Part A and Part B). In Part A, 7 people got VRC01LS. In Part B, 7 people (up to 10 people) will get VRC07-523LS. People were put in Part A first and now Part A of the study is done. People will now be put in Part B. If you agree to take part in this study (Part B), you will get VRC07-523LS only and we will measure the amount of the drug in your body and how much stays in your body over time. We will check to see if your immune system makes antibodies against the product you get.

About 14 to 20 people (7 to 10 people in each part) will take part in this study at the NIH Clinical Center in Bethesda, Maryland and sites within in the ACTG Network. The study will include a total of 23 clinic visits per person over a period of about 11 months.

After you complete the day 14 study procedures, we strongly advise that you start the antiviral therapy prescribed by your primary HIV physician (not study-provided).

**STUDY PRODUCTS**

VRC01LS and VRC07-523LS are study products that contain monoclonal antibodies. "Monoclonal" means that all the antibodies in each product are the same. These antibodies target the virus that causes HIV infection. As of May 10, 2018, approximately 60 people have received one of these antibodies and have not had any serious side effects or safety concerns.

VRC01LS and VRC07-523LS are based on an antibody that was first found in an HIV infected person. Both of these study products were developed by the Vaccine Research Center (VRC), NIH and made in a drug manufacturing laboratory. There are currently research studies of these products in adults without HIV infection. This is the first study to give VRC01LS or VRC07-523LS people with HIV infection.

There is currently no cure for HIV. We do not expect the products in this study to cure or control your HIV.

In laboratory and animal studies, VRC01LS and VRC07-523LS were shown to attach to and inactivate many types of HIV viruses. It is not known if the products will act the same way when given to humans. It will take many studies to learn if the products are useful for preventing or treating HIV. This study alone will not answer this question.

**SCREENING VISIT**

If you decide to join this study, you will be asked to sign this consent form. After you have signed the form, you will be asked some questions and will undergo some tests at the screening visit to see if it is safe for you to join the study.

At the screening visit you will have a physical exam. You will be asked about your medical history, including your HIV history, any medicines you have taken in the past and are currently taking, and if you have ever received antibodies directed against the HIV virus or taken any anti-HIV medicines. We will draw about 6 tubes of blood from you for routine blood tests, tests for Hepatitis B virus or Hepatitis C virus infection, tests for HIV antibodies and viral load (the amount of HIV in your blood), and $CD4^+/CD8^+$ T cell count (cells in your blood that fight infection). You will be informed if any tests show a medical problem. You will be advised if results show that you should seek medical care. Some medical conditions may make you not eligible for a clinical trial of an investigational product.

If you are female and able to become pregnant, you will have a pregnancy test done to see if you are pregnant. You cannot participate in this study if you are pregnant. If you are not pregnant or you are having sex that could lead to pregnancy, you will be asked and must agree to use birth control before you are able to participate in this study. We will discuss effective birth control methods with you.

**ELIGIBILITY**

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

- 18 to 70 years old
- HIV infected, have never taken antiretroviral (ARV) medications, but otherwise in good general health
- Under the care of a primary care provider for management of HIV
- Willing to let the study team give your lab test results to your primary care provider while you are in this study.
- Willing to receive VRC07-523LS
- Willing to donate blood samples for future research
- Willing to use birth control for the whole study, if you are able to become pregnant

**STUDY PROCEDURES**

Study product infusion: If you agree to enroll in this study, you will get one dose of VRC07-523LS. The exact dose you get will depend on much you weigh.

Before you are given the study product, your temperature, blood pressure, heart rate, and weight will be taken. You may also have a brief physical exam. If you are female and able to become pregnant, you must use an effective form of birth control for the entire study. A pregnancy test will be done to see if you are pregnant. If you are pregnant, we will not give you the study product.

VRC07-523LS will be given to you by intravenous (IV) infusion. This means we will place a thin tube or IV line into a vein in your arm. The IV line will be attached to a bag that contains the study product mixed with a liquid called "normal saline" or salt water. It will flow into your vein for about 30 minutes. If you have side effects during the infusion, it will be slowed or stopped as needed. You will be observed for at least 30 minutes immediately after receiving the study product.

If possible, we will also place an IV line in your other arm to collect blood samples. We will draw your blood before and right after the infusion, then at least 5 more times over the next 4 hours from this IV line. There are other blood draws at 8, 12 and 36 hours after infusion, which are optional. At least one IV line will stay in your arm for several hours. You will not lose any benefits if you choose not to give the optional blood samples. If you choose to get these blood draws, you may be admitted to the hospital for an overnight stay. The hospital stay is for convenience only and not to give you care or treatment.

We will give you a thermometer and ask you to check your temperature every day for 3 days after you get the study product. You will need to record your temperature and any symptoms you may have. Even if you do not feel sick, it is still very important that you record this information. You will get a password to a secure website to enter this information on an electronic form or "diary". If you do not have a computer, you may use a paper diary instead.

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

Follow-up visits: After you get the study product, you will need to come back to the clinic 11 times over a 4-week period. During the next 9 months, you will have 10 more follow-up visits.

At most visits, we will check you for any health changes or problems. Your temperature, blood pressure, and pulse will be taken and you will have a physical exam. We will ask you how you are feeling and if you have taken any medications. While you are in the study, we will also provide counseling about preventing pregnancy as well as positive-prevention counseling to help prevent illness and promote good health.

We will draw about 1 to 11 tubes of blood from you at each visit, depending on the type of visit. We will also ask you to provide a urine sample for a urine test at most visits. We will tell you right away if any of your test results show a health problem. You might need to have extra clinic visits and laboratory tests if you have health changes that need to be checked. The total amount of blood we draw from you will meet NIH guidelines.

We will use some blood samples to see how long the study product remains in your body and if your immune system makes antibodies against it. Results of these tests are not for checking on your health and we will not give you these results. We may also use some blood samples to check the level of ARV medications in your blood while you are in this study.

Research studies follow a set schedule. This helps us answer the research questions. The visit schedule is a little flexible, but it is important that you work with the staff to follow the schedule as closely as possible. You should try not to miss any visits. You should contact the clinic staff as soon as possible if you need to change the date or time of any visit.

For the entire duration that you are on study, which will be 48 weeks or about 11 months, a maximum of about 922 mL (or about 2 pints) of blood will be collected.

**HIV TESTING AND MANAGEMENT**

As you take part in this study, you will have frequent testing of your HIV viral load and CD4+ T cell count for research purposes. These tests will be given to you and sent to your primary care provider. You should discuss these results and any questions about management of your HIV infection with your primary care provider.

This study does not include standard medical care or the management of your HIV infection. The U.S. Department of Human Services and the clinical research team recommend that all HIV-infected individuals take (ARV) medication to reduce the chance of getting sick from HIV, increase life expectancy with HIV infection and prevent the spread of HIV to others.

We will not give you ARV medications as part of this research study. You must have a primary health care provider for HIV to take part in this study. If you do not have one and need help finding one or getting ARV medications, please tell a study doctor or nurse. We will help you find a qualified HIV doctor and ARV medications. You and your primary health care provider will make all decisions about starting, stopping or changing ARV medications. However, we strongly advise that you start ARV medications after you have completed the day 14 study procedures. We expect you to tell us about changes in your ARV medications. We do not expect VRC07-523LS to control HIV by itself. You should not change or stop ARV treatment without talking about it with your primary care provider. Changes in ARV treatment will not affect your continued participation in the study.

**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, study product infusions may be delayed or canceled.

**GENETIC TESTING**

In the future, genetic research tests may be done on your stored samples to help understand how VRC07-523LS works and interacts with your body. In research studies, genetic tests are done to see if different types of immune response are related to genetic differences in people; this includes testing your antibody genes. Genetic tests done in a research lab from your stored samples will not be recorded in your medical record and will not have your name on the sample. The performance of these tests is not for health care purposes.

HLA type is a genetic test. People with certain HLA types might be more likely to develop certain diseases. Simply having those HLA types does not mean they will develop those diseases. HLA typing can reveal family relationships. It is our policy not to discuss your HLA results unless they have direct medical or reproductive implications for you or your family. Genetic information about you will not be revealed to others, including your relatives, without your permission. We will not release any information about you or your family to any insurance company or employer unless you sign a document allowing release of information.

HLA typing may be ordered through the NIH Clinical Center medical laboratory. If performed at the NIH Clinical Center, your HLA type results will be in your medical record.

HLA typing may be ordered through the NIH Clinical Center medical laboratory. If performed at the NIH Clinical Center, your HLA results will be in your medical record.

**STORED SAMPLES**

We will collect blood samples 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 done with your stored samples will not be in your medical record or reported to you.

Some of your blood samples that are left over after all required study testing are done may be stored and used for VRC-approved and ACTG-approved HIV-related research.

**Labeling of Stored Samples:** We will label your stored samples by a code (like a number). Only the study team can link this code to you. Any identifying information about you will be kept confidential as much as the law allows. 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; in the ACTG or outside of the ACTG) 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 can only take part in this study if you agree to let us collect, store, and use your blood samples in future unspecified 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 of Blood Drawing and IV insertion: The risks of drawing from a vein and having an IV include pain, bruising, bleeding, lightheadedness and fainting. Rarely, infection or inflammation can occur in the skin or vein. Blood clots are possible risks when using an IV for blood draw.

Risks of VRC07-523LS: This study is the first time that VRC07-523LS is being given to people with HIV infection. As of January 2018, the people who have received at least one dose of VRC07-523LS had no concerning reactions to the

product. VRC07-523LS may have other unknown risks or side effects We do not know if getting VRC07-523LS will affect how you respond to any similar monoclonal antibody against HIV.

General risks of monoclonal antibodies: Side effects to infusions of monoclonal antibodies 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 product is infused. If you have symptoms while you get VRC07-523LS, tell the nurse right away. Slowing or stopping the infusion may help improve these symptoms. Side effects may also include reactions at the injection site, such as redness, bruising, and swelling.

Some antibody products have a risk of serious allergic reactions or cytokine release syndrome 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.
- Cytokine release syndrome can happen when an antibody targets a cell protein that triggers immune cells to release cytokine (proinflammatory molecules in your body).

All of these reactions are very unlikely because VRC07-523LS is a fully human antibody that attacks the HIV virus, and not your cells.

In addition to the possible risks that are listed above, the study products may have other side effects that we do not know about yet. Taking part in this study may affect your eligibility for future studies of other investigational monoclonal antibodies, antibody mixtures and other similar products.

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 during Pregnancy: We do not know what effects the study products may have on a fetus or nursing infant. Women must agree not to get pregnant during the study. We will discuss effective birth control methods with you. If you are able to become pregnant, you and your partner must use reliable birth control from the time you start the study until you complete the last study visit.

If you can become pregnant, you must have a pregnancy test before you enter this study. The test must show that you are not pregnant. You must tell the clinic staff right away if you become pregnant during this study or think that you might be pregnant. If you become pregnant after getting the study product, 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). This report will not use your name or other information that could be used to identify you.

**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 YOUR PARTICIPATION**

There are no costs to you for taking part 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. It is possible that you may have some expenses that are not covered by the study compensation provided.

**COMPENSATION TO YOU FOR YOUR PARTICIPATION**

You will be compensated for your study participation as follows:

The compensation is $175 for outpatient scheduled visits including blood drawing. Compensation for IV product administration visit and follow-up blood sample collections within the first 24 hours after administration will be compensated at a combined amount of $600. Compensation for timely completion of all 3 days of an electronic diary will be $25 total. Compensation for visits that do not include blood drawing is $75.

Total compensation for completion of the study is estimated to range from $4275 to $4300. Actual compensation is based on the number and type of study visits you complete. Your compensation will be reported to the Internal Revenue Service as taxable income.

**REASONS FOR REMOVING YOU FROM THE STUDY WITHOUT YOUR CONSENT**

You may be removed from the study 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 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 you will be told the reason why.

You may choose to stop taking part in the study at any time.

If you received the study product before you discontinue the study early, you will be asked to continue to be part of the study and return for the rest of the study visits At the visits you will have some tests performed for safety monitoring, however samples for research purposes will not be collected.

**ALTERNATIVES**

This study is not designed to treat or prevent HIV infection or any disease. You may choose to not take part in this study. You may be eligible for other studies. Instead of being in this study you have the choice of:

- Treatment with prescription drug available to you
- Treatment with experimental drugs, if you qualify
- No Treatment

**CONFLICT OF INTEREST**

The research staff are reviewed at least yearly for conflicts of interest. You may ask the research team for additional information.

The National Institutes of Health, including some members of the Vaccine Research Center scientific staff, developed the experimental product in this research study. The results of this study could play a role in whether the FDA will approve the experimental product for sale at some time in the future. If approved, the future sale of the vaccine 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 get any money from the development or sale of the product.

This protocol 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.

**CLINICALTRIALS.GOV**

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*. This web site 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, National Institute of Allergy and Infectious Diseases institutional review board, study monitors 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 National Institutes of Health, 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 National Institutes of Health policies.

**4. Problems or Questions.** If you have any problems or questions about this study or about any research-related injury, contact the Principal Investigator, [redacted], or the Study Coordinator, [redacted] at 301-451-8715.

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:**

**A. Adult Patient'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.

Signature of Adult Patient/Legal Representative _____ Date _____

Print Name _____

**B. Parent's Permission for Minor Patient.**

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.
(Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s)/Guardian _____ Date _____

Print Name _____

**THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM MAY 07, 2018 THROUGH MAY 06, 2019.**

Signature of Investigator _____ Date _____

Print Name _____

Signature of Witness _____ Date _____

Print Name _____